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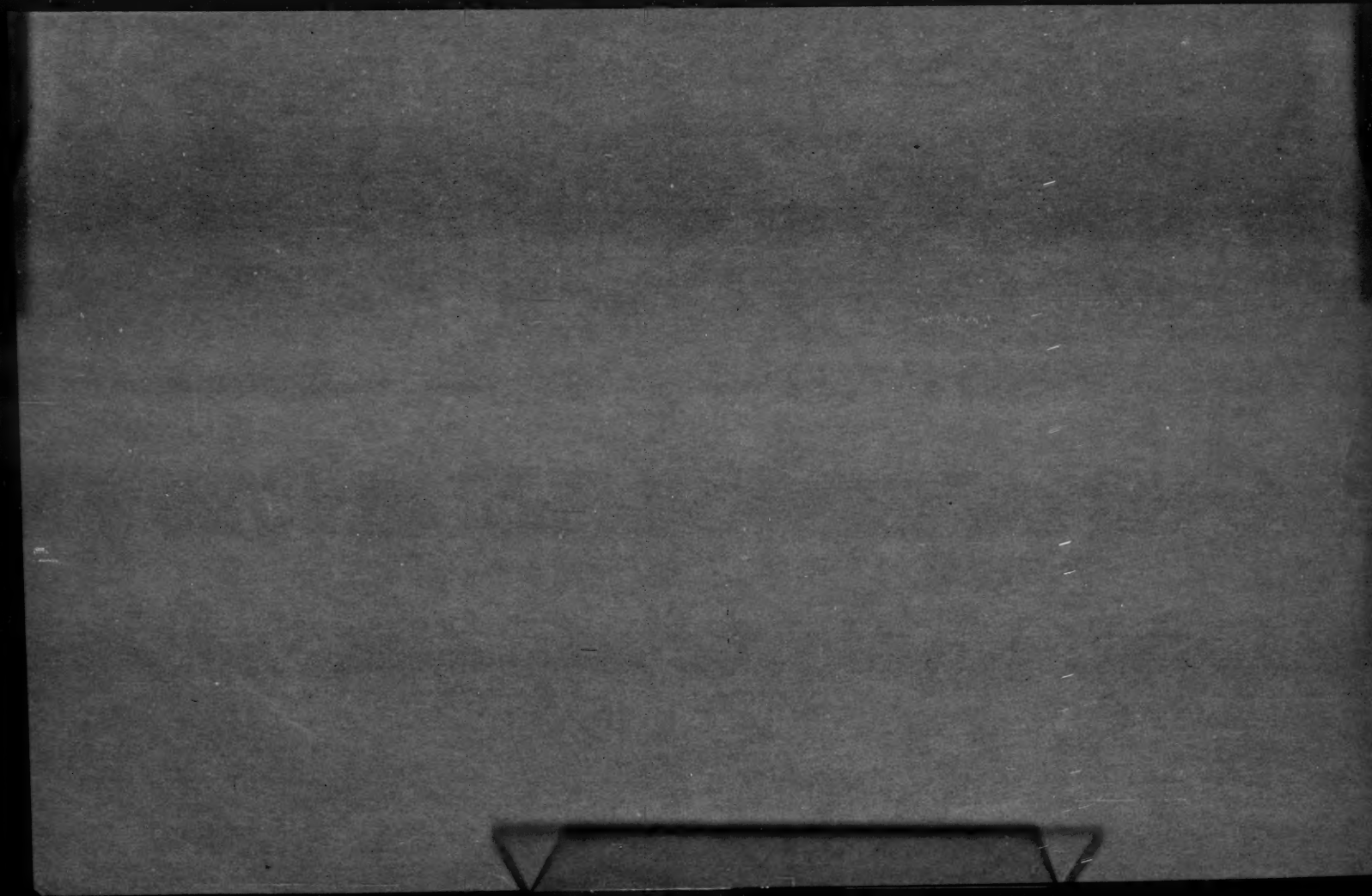

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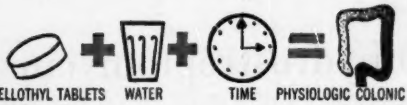
1. Gastroenterology *13*:275 (Oct.) 1949. 2. N. Y. State J. Med. *48*:1822 (Aug.) 1948.



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Smadel, J. E.: J.A.M.A. *142*:313, 1950 (discussion)

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Hewitt, W. L., and Williams, B., Jr.: New England J. Med. *242*:119, 1950

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Payne, E. H.; Knaudt, J. A., and Palacios, S.: J. Trop. Med. & Hyg. *51*:68, 1948

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Ley, H. L., Jr.; Smadel, J. E., and Crocker, T.: Proc. Soc. Exper. Biol. & Med. *68*:9, 1948

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1. Best, R. R.: Ann. Surg. *128*: 348 (Sept.) 1948.

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1. Beckman, H.: Treatment in General Practice. Philadelphia, Saunders, 5th ed., 1946, 784-785.
2. Beckman, H.: Treatment in General Practice. Philadelphia, Saunders, 6th ed., 1948, 744.

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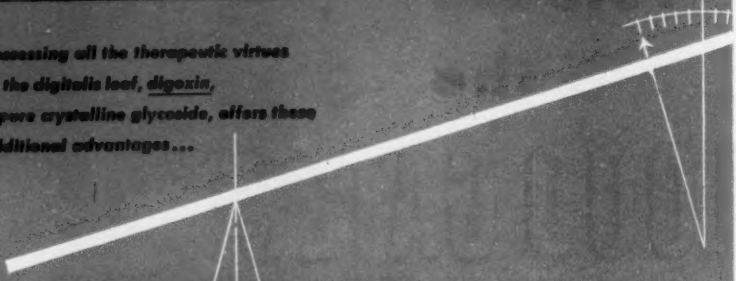

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ASPIRATION BIOPSY OF BONE MARROW AS AN AID IN DIAGNOSIS OF HISTOPLASMOSIS

Report of a Case

PEYTON T. PRATT, M.D.

STEVEN O. SCHWARTZ, M.D.

AND

LEE EHRLICH, M.D.

CHICAGO

MEDICAL history is replete with examples of diseases previously unknown that suddenly became commonplace. In the case of infectious diseases there is always an element of doubt whether the malady is actually becoming more widespread or is simply being more widely recognized. Evidence gleaned from experience with noninfectious diseases points to the latter possibility. So it seems with histoplasmosis. Between the first description by Darling [1] in 1906 and the review of the subject by Parsons and Zarafonetis [2] in 1945, only 71 cases were reported. Yet, from 1945 to 1949 an additional 42 cases [3] of proved

From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital.

Aided by grants from the Olivia Sue Dvore and Robert L. Goldblatt Foundations and the Wilson Laboratories.

1. Darling, S. T.: A Protozoöan General Infection: Histoplasma Capsulatum Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen and Lymph Nodes, J. A. M. A. **46**:1283 (April 28) 1906.

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3. (*a*) Alonso, J. M., and Cancela Freijo, J.: Histoplasmosis de Darling: Primera observación efectuada en el Uruguay; Curacion clinica luego de tratamiento con sulfadiazina (nota preliminar), Arch. urug. de med., cir. y especialid. **24**:193, 1944. (*b*) Balina, P. L.; Herrara, J. A.; Bosq, P., and Negroni, P. B.: Tercer caso argentino de histoplasmosis, Rev. argent. dermatosif. **27**:453, 1943. (*c*) Beamer, P. R.; Reinhard, E. H., and Goodof, I. I.: Vegetative Endocarditis Caused by Higher Bacteria and Fungi, Am. Heart J. **29**:99, 1945. (*d*) Boltjea, B.: Histoplasmosis: Report of a Case and Brief Review of the Literature, J. Kansas M. Soc. **44**:226, 1943. (*e*) Casas Carnicero, J., and Velasco Alonso, R.: Histoplasmosis, Gac. méd. españ. **19**:344, 1945. (*f*) Cassidy, J. E.: Histoplasmosis, Clin. Proc. Child. Hosp. **1**:168, 1945. (*g*) Catanei, A., and Kervran, P.: Nouvelle mycose humaine observée au Soudan français, Arch. Inst. Pasteur d'Algérie **23**: 169, 1945. (*h*) Conlin, F. M., and Hankins, C. R.: Histoplasmosis: A Case Report, Nebraska M. J. **32**:101, 1947. (*i*) Curtis, A. C., and Grekin, J. N.: Histo-

(*Footnote continued on next page*)

histoplasmosis have been recorded, and there are those who feel that the disease is sufficiently common to be responsible for much of the pulmonary calcification previously attributed to tuberculosis.[4]

The protean manifestations of histoplasmosis make diagnosis difficult, and neither in vivo (skin) nor in vitro (precipitin) tests have been found completely satisfactory for diagnostic purposes. So far, the demonstration of the Histoplasma capsulatum, in tissues or in culture, has been necessary before the diagnosis could be accepted. In cases in which lesions are available for biopsy, this is not too difficult, but in the systemic form of the disease the search for a satisfactory diagnostic method continues. Our recent experience, together with that previously described in the literature, suggests that the marrow is of unusually great diag-

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plasmosis, Review of Cutaneous and Adjacent Mucous Membrane Manifestations with Report of 3 Cases, J. A. M. A. **134**:1217 (Aug. 9) 1947. (*j*) German, W. K.; Ashmun, S., and Dille, C. E.: Histoplasmosis, Am. J. Clin. Path. **13**:12, 1943. (*k*) Iams, A. M.; Tenen, M. M., and Flanagan, H. F.: Histoplasmosis in Children: Review of Literature, with Report of a Case, Am. J. Dis. Child. **70**:229 (Oct.) 1945. (*l*) Johnson, H. E., and Batson, R.: Benign Pulmonary Histoplasmosis, Dis. of Chest **14**:517, 1948. (*m*) Kemper, J. W., and Bloom, H. J.: Histoplasmosis: Report of a Case, J. Oral Surg. **2**:167, 1944. (*n*) Kunstadter, R. H.; Whitcomb, F. C., and Milzer, A.: Primary Histoplasmosis with Recovery of Histoplasma Capsulatum from the Blood and Bronchial Secretions, J. Lab. & Clin. Med. **34**: 1290, 1949. (*o*) Kuzma, J. F., and Schuster, M.: Histoplasmosis, Reticuloendotheloid Cytomycosis, Wisconsin M. J. **45**:591, 1946. (*p*) Lam, F. K., and Price, S.: Histoplasmosis in Man, Hawaii M. J. **6**:313, 1947. (*q*) Martin, W. P., and Silher, B.: Histoplasmosis of Darling, Am. J. Clin. Path. **14**:119, 1944. (*r*) McLeod, J. H.; Emmons, C. W.; Ross, S., and Burke, F. G.: Histoplasmosis: A Report of Four Cases, Two in Siblings, J. Pediat. **28**:275, 1946. (*s*) Mider, G. B.; Smith, F. D., and Bray, W. E., Jr.: Systemic Infection with Cryptococcus Neoformans (Torula Histolytica) and Histoplasma Capsulatum in the Same Patient, Arch. Path. **43**:102 (Jan.) 1947. (*t*) Miller, H. E.; Keddie, F. M.; Johnstone, H. G., and Bostik, W. L.: Histoplasmosis: Cutaneous and Mucomembranous Lesions, Mycologic and Pathologic Observations, Arch. Dermat. & Syph. **56**:715 (Dec.) 1947. (*u*) Pera, M.: Histoplasmosis in Brazil, Am. J. Trop. Med. **26**:273, 1946. (*v*) Stuart, B. M.; Gardner, J. W.; LeMone, D. V., and Von Ravenswaay, A. C.: Pulmonary Histoplasmosis, J. Missouri M. A. **45**:417, 1948. (*w*) Swan, L. L., and Finnegin, J. V.: Histoplasmosis: Report of a Case with Autopsy, Wisconsin M. J. **45**:763, 1946. (*x*) Thomas, W. A., and Mitchell, J. H.: Histoplasmosis, Am. J. Med. **2**:538, 1947. (*y*) Weed, L. A.; Iams, A. M., and Keith, H. M.: Histoplasmosis in Infancy: Pathologic Picture as Seen in One Case, Arch. Path. **43**:155 (Feb.) 1947. (*z*) Weed, L. A., and Parkhill, E. M.: Diagnosis of Histoplasmosis in Ulcerative Disease of the Mouth and Pharynx, Am. J. Clin. Path. **18**:130, 1948. (*a'*) Wohlwill, F., and Morais David, A.: Histoplasmose de Darling, Lisboa méd. **20**:403, 1943. (*b'*) Worgan, D. K.: Histoplasmosis: A Summary of the Known Facts About the Disease, Bull. School Med. Univ. Maryland **30**:69, 1945. (*c'*) Ziegler, E. E.: Histoplasmosis of Darling: Review and Case Report with Autopsy, Ann. Int. Med. **24**:1073, 1946.

4. Palmer, C. E.: Non-Tuberculous Pulmonary Calcification and Sensitivity to Histoplasmosis, Pub. Health Rep. **60**:513, 1945.

nostic value, since it offers a site from which material is readily available for both a direct study af the organism and its culture.

This communication presents a case in which H. capsulatum was demonstrated ante mortem in both the blood and the marrow directly and by culture. The literature relative to the value of this diagnostic method is reviewed in an attempt to evaluate the frequency with which these sources might be utilized for diagnostic purposes.

REPORT OF CASE

D. M., a 70 year old Russian-born Jewish man, was admitted to the Cook County Hospital on Aug. 22, 1949. The history was obtained in most part from his landlord because the patient was somewhat confused and unresponsive and did not speak English well. He had lived in Chicago for many years and was a scavenger and peddler, handling old clothes, trinkets and junk. He had been weak, had not eaten and had been drinking intoxicating beverages for several months. Emotional instability, manifested by his screaming at persons without apparent reason, had been noted recently. A productive cough of several months' duration, more pronounced in the evenings, was the only other symptom.

He was well developed, though emaciated and dehydrated. There was generalized bronzing of the skin except for the "shoe area." The blood pressure was 110 systolic and 70 diastolic, the pulse rate 80, the temperature 98 F. and the respiration rate 22. The tongue was beefy red and dry and smooth along the edges and tip. Dental caries and pyorrhea were conspicuous. The chest was slightly emphysematous. There was decreased resonance to percussion in the upper lobe of the left lung anteriorly and in the lower lobe of the right lung posteriorly, where the breath sounds were also increased. Moist rales were heard in scattered areas throughout the posterior pulmonary fields, mostly over the lower lobe of the right lung. No abnormalities were noted in the heart. The liver was palpable 3 cm. below the costal margin in the right midclavicular line. The spleen was not palpable. Neurologic examination disclosed no abnormality.

Laboratory studies showed 58 per cent (9 Gm. per hundred cubic centimeters) hemoglobin, 3,010,000 red blood cells and 2,500 white blood cells, with 78 per cent segmented neutrophils, 12 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils. The red blood cells were normochromic, with moderate anisocytosis and slight poikilocytosis. Blood platelets (thrombocytes) were diminished in number. The urine was amber and had a specific gravity of 1.012, with no albumin, sugar or abnormal sediment. Reactions for urinary urobilinogen and bile were 4 plus. Total protein measured 5.2 Gm. (albumin, 3.2 Gm.; globulin, 2 Gm.) and inorganic phosphorus, 4.1 mg. per hundred cubic centimeters. Alkaline phosphatase was 7.3 and acid phosphatase 0.1 Bodansky units; chlorides were 105.6 and sodium 143.7 milliequivalents per liter, with 20.3 mg. of potassium per hundred cubic centimeters. Nine days after his admission the patient had 53 per cent (8.2 Gm.) hemoglobin, 2,650,000 red blood cells and 3,000 white blood cells, with 52 per cent segmented neutrophils, 20 per cent lymphocytes, 24 per cent monocytes and 4 per cent eosinophils. The urine now gave a 2 plus reaction for urobilinogen and bile; cephalin flocculation was 3 plus and thymol turbidity 12.1 units. Total cholesterol measured 71 mg. per hundred cubic centimeters (with 56 per cent esters). The icterus index was 11 units. There was no free acid in the gastric contents a half-hour after injection of histamine.

Roentgenologic examinations revealed the heart to be normal, the presence of a small round soft opaque density in the left upper pulmonary field, no abnormality of the skull and a moderately radiolucent area in the semilunar bone, with cystic changes in the head of the first metacarpal bone of the right hand.

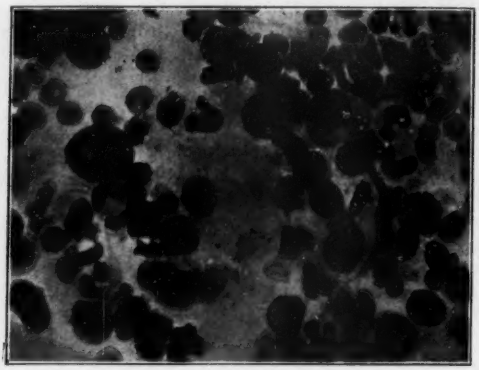

Fig. 1.—Histoplasma capsulatum organism in a histiocyte. Specimen, obtained by marrow aspiration.

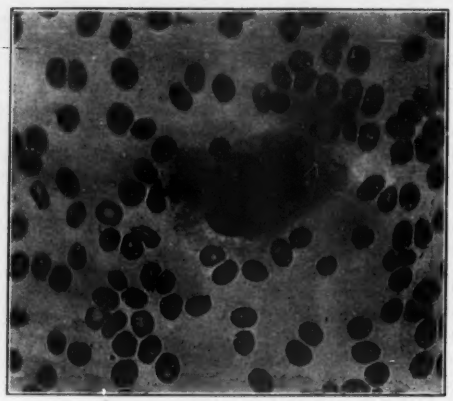

Fig. 2.—Histoplasma capsulatum organism in a monocytoid cell from peripheral blood.

The biopsy specimen of sternal marrow, obtained by aspiration, was moderately hypercellular with adequate numbers of megakaryocytes. The ratio of nucleated red blood cells to nucleated white blood cells was 1:2. There were occasional pernicious anemia type band cells and rare pernicious anemia type rubricytes and metarubricytes. The striking feature, however, was the great increase in histio-

cytes, many of which contained from one to twenty organisms in their cytoplasm. These were identified morphologically as H. capsulatum (fig. 1). A review of the peripheral blood films also revealed the fungus in the cytoplasm of an occasional monocyte (fig. 2). Marrow was obtained for culture the following day and the tuberculate chlamydospores of H. capsulatum were demonstrated on Littman's medium (fig. 3). The fungus was also readily grown from the blood in brain broth.

The patient was treated with penicillin and multiple vitamin preparations. In spite of the administration of penicillin, the temperature fluctuated between normal and 102 F. Because of the finding of pernicious anemia type red and white blood cells in the marrow, he was also given liver extract parenterally on September 2, but he died on September 3.

Postmortem Examination (four days after death).—Gross Observation: Gross examination revealed the body to be emaciated though well developed. The skin

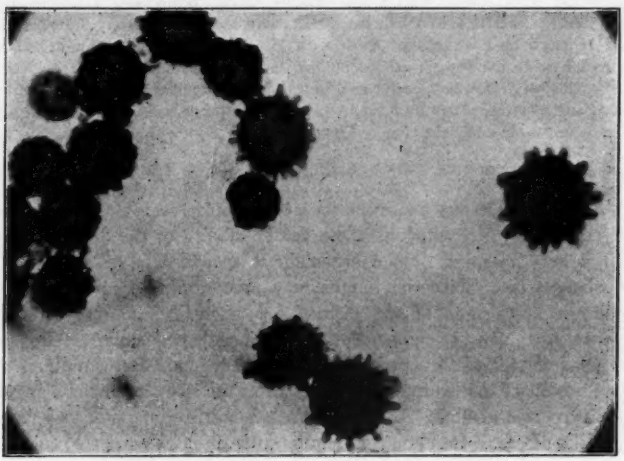

Fig. 3.—Tuberculate chlamydospores of Histoplasma capsulatum obtained from culture of blood and bone marrow.

was bronzed except for the "shoe area." There was a traumatic deformity of the right thumb. The liver extended 6.5 cm. below the xiphoid and right costal margin. The lower pole of the spleen was at the costal margin in the left midaxillary line. There were focal fibrous adhesions in both pleural cavities. The lungs were heavier than normal and all the lobes were subcrepitant. On cut section the surface was mottled purplish red, moist and firm. In the upper lobe of the left lung there was a circumscribed gray-yellow caseous necrotic area measuring 0.5 cm. in diameter, surrounded by several grayish tan translucent nodules measuring about 1 mm. A few similar nodules were scattered throughout both pulmonary fields. The spleen weighed 620 Gm. and measured 20 by 11 by 8 cm. Several gray-tan translucent circumscribed nodules, measuring 1 to 5 mm. in diameter, were seen on its cut surface. The liver weighed 2,200 Gm., the capsule was thin and smooth, the edge rounded. There were a few adhesions between its upper pole

and the diaphragm. Cut sections of the liver revealed it to be yellow-tan and pale, with bright red prominent lobular centers. The heart, pancreas, adrenal glands, kidneys and brain were grossly not unusual. The prostate was slightly enlarged, firm and nodular. The gastric mucosa was smooth and atrophic. The marrow was red and hyperplastic.

Microscopic Examination: Sections from the lung revealed a generalized proliferation of histiocytes. Large granulomas, made up of plasma cells, lymphocytes, fibroblasts, epithelioid cells, histiocytes and Langhans' giant cells, were observed in several areas. These granulomas were more vascular than fresh tubercles and some had undergone caseous necrosis. The fungus was seen in both the histiocytes and the giant cells. In the sections examined the general architecture of the spleen and lymph nodes was intact. However, there were small accumulations of histiocytes scattered throughout, some of which contained H. capsulatum. The architecture of the liver was also preserved. There was a definite increase in the size of the portal fields, with a few delicate fibrous projections extending from them. In the central area the hepatic cells were almost completely destroyed and were replaced by macrophages laden with H. capsulatum. In the midzonal and periportal areas the hepatic cells contained large fat globules in their cytoplasm. The fungus was also occasionally seen in the macrophages of the pancreas, adrenal glands and marrow. It stained bright red with Mallory's stain, dark blue with the Goodpasture stain and light blue by Custer's method.

COMMENT

The multitudinous manifestations of histoplasmosis make its clinical diagnosis extremely difficult unless the possibility of the disease is constantly kept in mind or the organism is accidentally discovered in a biopsied tissue. Since the fungus may involve almost any organ, the symptoms and signs of the disease are legion. The most frequent observations are splenomegaly, hepatomegaly, anemia, leukopenia, irregular elevations in temperature, pulmonary signs and symptoms and oral lesions. Thus, lymphomas, cirrhosis of the liver, pernicious anemia, pulmonary tuberculosis, Addison's disease and carcinomatous or granulomatous ulcers of the mouth are among the diseases simulated.

Our case presented many of the typical signs of this atypical disease. The unexplained anemia and leukopenia prompted the marrow examination. There were also hepatomegaly, irregular fever and pulmonary findings. The spleen, though large, was not palpable during life. Yet, with all these signs, the diagnosis could not have been made without the demonstration of the fungus. The malnutrition and the extensive hepatic damage may have been responsible for the production of the pernicious-anemia-like changes in the marrow, though true pernicious anemia could not be ruled out since the patient had histamine-resistant gastric achlorhydria and died before the liver therapy could elicit a reticulocyte response.

There have been described 113 cases of histoplasmosis proved by biopsy or autopsy, excluding ours. Most of these, except the ones in which there were external lesions, have presented diagnostic problems.

Even when the disease is suspected, it is difficult of proof. That the marrow might be an unusually fruitful site for biopsy is suggested by the fact that of the 23 cases [5] in which examination of the marrow was reported H. capsulatum was found in 11.[6] The recovery and identification of the organism could probably be accomplished even more frequently by culture of the marrow in suspected cases.[7] The discovery of the organism in the peripheral blood represents somewhat of a curiosity, having been reported but five times [8] in the past. Mider and his associates [3s] suggested and showed that concentrated leukocyte smears of peripheral blood may be of additional help in demonstrating the fungus.

The almost universal coexistence of splenomegaly and leukopenia in the disease probably represents a cause and effect relationship—another example of functional hypersplenism secondary to a diseased spleen.

SUMMARY

A case of histoplasmosis of Darling is reported in which the Histoplasma capsulatum was morphologically and culturally demonstrated ante mortem in both the marrow and the blood.

Aspiration biopsy of marrow promises to become an important diagnostic aid in suspected cases of histoplasmosis.

Dr. Oscar Felsenfeld and Miss Carrie Woolsey aided in the identification and culture of the Histoplasma capsulatum.

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5. (*a*) Footnote 3 *a, c, e, i, m, r, s, t* and *y*. (*b*) Parsons and Zarafonetis.[2] (*c*) Davis, H. V., and Neff, F. C.: Histoplasmosis in Infancy, Am. J. Dis. Child. **71**:171 (Feb.) 1946. (*d*) Schlumberger, H. G., and Service, A. C.: A Case of Histoplasmosis in an Infant with Autopsy, Am. J. M. Sc. **207**:230, 1941.

6. Footnote 3 *a, r, s, t* and *y*. Davis and Neff.[5c] Parsons and Zarafonetis.[2] Schlumberger and Service.[5d]

7. Culbertson, C., Jr.: Personal communication to the authors.

8. Mider and others.[3s] Parsons and Zarafonetis.[2]

SYNDROME CHARACTERIZED BY GLOMERULONEPHRITIS AND ARTHRITIS

Libman-Sacks Disease with Predominantly Renal Involvement

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IN RECENT years we have studied an unusual group of cases to which we wish to draw attention. They show certain interesting similarities from both the clinical and the pathologic standpoint. The clinical courses in these cases and the terminal pictures have been such that we feel they constitute a definite, recognizable syndrome. The features these patients exhibited in common were an arthritis of varying duration, the subsequent development of albuminuria of rather marked degree, nephrotic edema, subsequent renal insufficiency and, finally, a fatal outcome with the pathologic findings of a subacute type of glomerulonephritis.

The arthritis was the initially recognizable feature of the disorder. It was nonspecific in nature and characterized by pain, tenderness, stiffness, redness and swelling of the small and medium-sized joints. These symptoms were migratory, of mild or moderate intensity and transient, and they disappeared without leaving discernible permanent damage. In this stage no definite diagnosis could be made, and the condition was considered to be "symptomatic" rheumatism. In some instances there was troublesome thoracic pain of an indefinite character.

The first evidence of a renal disorder noted in each instance was albuminuria. This was generally associated with the presence of a few casts, erythrocytes and leukocytes in the urinary sediment. The subsequent onset of nephrotic edema, with decreased values for serum albumin and elevated values for plasma cholesterol, was then followed in a few weeks to a few months by the development of severe, rapidly progressing renal insufficiency with features typical of this state. Of the 4 cases in which permission for necropsy was granted, the pathologic findings were those of subacute glomerulonephritis in 3 and chronic glomerulonephritis in 1.

From the Division of Medicine (Dr. Daugherty) and the Section on Pathologic Anatomy (Dr. Baggenstoss), Mayo Clinic.

Few reports of cases of this type have been found. Osler [1] cited a case of Dr. W. T. Watson which showed certain similar features. A 10 year old girl suffered from abdominal pain, arthritis and erythematous lesions of the skin, and subsequently nephritis developed. Within a month she had anasarca and anuria. At necropsy the kidneys were large and pale. The malpighian tufts were compressed by the new growth of a mass of cells in the area of the capsular space which formed a crescentic mass.

Tremaine [2] reported 2 cases which he termed "Subacute Pick's Disease with Polyarthritis and Glomerulonephritis." In 1 of these cases the patient had thoracic pain, fever, chills and articular pains. Some months later this patient presented the picture of nephrosis characterized by massive edema, ascites, a normal blood pressure and a reversal of the albumin-globulin ratio. At necropsy the kidneys were slightly enlarged. The glomeruli were damaged; the process involved the cells of the endothelium, which were swollen and surrounded by delicate hyaline deposits. The epithelial cells of the tubules contained fat droplets and hyaline deposits about their basement membranes.

Recently Brenner, Leff and Hochstein [3] have reported a case which presents the features of this syndrome. Their case was considered to be one of lupus erythematosus disseminatus sine lupo and was described "because there are so few specific reports of the disease without the skin component." This excellent report, however, did not emphasize the fact that the renal lesion observed was very different from that seen in most cases of lupus erythematosus. Indeed, Keith [4] has stated: "In regard to the renal complications in lupus erythematosus: 1. Renal insufficiency does not play an important role in causing death, since severe chronic uremia very seldom occurs. 2. The histologic changes in the kidney are almost never as extensive as those seen in cases of progressive chronic glomerulonephritis of similar duration."

We wish to consider this group of cases as related to the diffuse disease described by Libman and Sacks [5] and to consider the possibility that it represents a distinct recognizable symptom complex of, or related

1. Osler, W.: On the Visceral Manifestations of the Erythema Group of Skin Diseases, Am. J. M. Sc. **127**:1-23 (Jan.) 1904.

2. Tremaine, M. J.: Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis: A Report of 2 Fatal Cases, New England J. Med. **211**:754-759 (Oct. 25) 1934.

3. Brenner, J. J.; Leff, W. A., and Hochstein, E.: Lupus Erythematosus Disseminatus Sine Lupo with the Nephrotic Syndrome, Am. J. Med. **5**:288-297 (Aug.) 1948.

4. Keith, N. M.: The Renal Problem in Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **15**:682-683 (Oct. 23) 1940.

5. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701-737 (June) 1924.

to, that disease. Obviously this problem will be resolved when the etiologic factors of Libman-Sacks disease and the group herein presented are known. Because of the unique nature of the syndrome it is felt that reporting of this group of cases is justified. It is hoped that it will add to the knowledge of one of the features, namely, the renal aspect of Libman-Sacks disease and to our knowledge of the so-called diffuse collagen diseases.[6]

REPORT OF CASES

CASE 1.—A student, aged 17 years, registered at the Mayo Clinic on Nov. 28, 1941 and was immediately hospitalized. The patient had been well until October 1940, when he noticed a mild degree of stiffness and tenderness of his ankles, knees, elbows, wrists and fingers. These rheumatic symptoms were migratory and disappeared in about four months. About Sept. 15, 1941 he noted edema of both lower extremities and a rapid gain of approximately 30 pounds (13.6 Kg.). Urinalyses showed albuminuria ranging from grade 2 to grade 4, a few casts and persistent microscopic hematuria and pyuria. On November 1 an acute febrile illness characterized by anorexia, nausea, vomiting and diarrhea developed.

At the time of admission to the clinic there was moderate pallor of the mucous membranes and moderate edema of the lower extremities and sacral region. The average of repeated determinations of blood pressure was 170 systolic and 100 diastolic. There was marked generalized narrowing of the retinal arterioles without evident sclerosis. Otherwise, the physical examination gave essentially negative results.

Urinalysis disclosed a specific gravity of 1.019; albuminuria, grade 4; a few waxy and granular casts, and a few erythrocytes and leukocytes. The hemoglobin content was 9.7 Gm. per hundred cubic centimeters; the erythrocyte count was 4,070,000 per cubic millimeter, and the leukocyte count was 6,600. The value for blood urea was 100 mg. per hundred cubic centimeters; for creatinine, 5.2 mg.; for serum sulfate, 10.8 mg., and for blood cholesterol, 292 mg. The total serum protein measured 3.4 Gm. and the albumin 2.1 Gm. per hundred cubic centimeters. A roentgenogram of the thorax showed no abnormalities. In this case, as in those following, other laboratory data are as shown in table 1.

The patient's course in the hospital was gradually downhill. There was an elevation of temperature to 101 F. on one occasion, immediately after a transfusion, but this occurred at no other time during the hospitalization. In the first twelve days he lost 9 pounds (4.1 Kg.) but considerable edema persisted. The ocular fundi showed evidence of increasing angiospasm. The value for blood urea rose to 242 mg.; for creatinine, to 10.2 mg., and for serum sulfate, to 18.4 mg. On the thirtieth hospital day the patient had two convulsions. During the second one pulmonary edema developed, and the patient died.

Necropsy.—The peritoneal cavity contained approximately 5,000 cc. of clear fluid, the right pleural cavity 50 cc., the left pleural cavity 200 cc. and the pericardial sac 200 cc. of clear fluid.

The heart weighed 400 Gm. (normal 345 Gm.). The valves all appeared normal except for a small area of thickening on the free border of the posterior leaflet of the mitral valve.

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6. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569-631 (Oct.) 1941.

TABLE 1.—*Laboratory Data*

Case	Urinary Sediment *			Urinary Protein, Gm./ 24 Hr.	Blood Urea † Mg./100 Cc.		Blood Creatinine, Mg./100 Cc.		Serum Sulfate, Mg./ 100 Cc.	Serum Potassium, Mg./ 100 Cc.	Serum Protein, Gm./ 100 Cc.		Plasma Cholesterol, Mg./ 100 Cc.	Total Plasma Lipids, Mg./ 100 Cc.	Blood Hemoglobin, Gm./ 100 Cc.	Leukocytes, No./ Cu. Mm.	Sedimentation Rate, Mm.	Blood Cultures	
	Albuminuria	Cylindruria	Erythrocyturia		Admission	Terminal	Admission	Terminal			Albumin	Globulin						No.	Result
1	4	2	2	15-25	100	242	5.2	10.2	18.4	27.5	2.1	1.3	292	.....	9.7-11.7	6,000	114	1	Neg.
2	4	0-1	1	1.6-8.2	28	164	...	2.1	10.8	23.3	1.5	1.8	327	1,005	10-15	5,200-13,400	131	4	Neg.
3	4	2	3	.....	42	468	...	10.4	9.9	34.9	2.1	2.1	370	1,402	7.0-13.1	2,500-10,700	146	5	Neg.
4	4	2	2	.....	178	192	7.2	8.4	....	....	2.9	1.6	...	.....	5.1- 5.5	7,000- 8,900	...	1	Neg.
5	3	0-1	3	.....	72	350	...	15.2	21.0	23.1	3.3	3.6	...	.....	7.0- 7.9	4,000-13,900	133	5	Neg.
6‡	4	0	3	.....	118	118	...	2.6	9.3	27.3	1.6	2.3	...	.....	5.4	3,000- 9,800	141	0	.....
7	4	1	2	5.4-13.3	58	156	1.2	2.6	16.6	20.3	2.1	2.1	453	1,337	10.2-11.9	5,900- 9,800	109	1	Neg.

* Graded on the basis of 1 to 4 (0 means none or absent).

† Urea as milligrams of urea, not milligrams of urea nitrogen (normal 10 to 40 mg.). (Urea nitrogen equals 46.6 per cent of urea.)

‡ Kline flocculation reaction, 1 plus; Kahn flocculation reaction, 3 plus; Kline flocculation reaction negative in all others.

Histologic Examination: In sections of the posterior leaflet of the mitral valve there was a focus of fibrinoid degeneration of the collagenous connective tissue involving the entire thickness of the leaflet and elevating the endothelium of the auricular surface. The fibroblasts, monocytes and polymorphonuclear leukocytes in this region were shrunken, with pyknotic and disintegrated nuclei. Adjacent to the area of fibrinoid degeneration there was a collection of polymorphonuclear leukocytes. A similar focus of fibrinoid degeneration and suppurative inflammation was found just distal to the ring of the mitral valve.

In sections of the kidneys no normal glomeruli could be found. There was an extensive increase in the number of endothelial cells which resulted in the production of very cellular glomerular tufts and the obstruction of many of the capillaries (fig. 1 *a*). Hyaline thrombi occluded some of the latter also. In a few of the glomeruli fusion, early fibrosis and occasionally complete fibrosis of the tufts were observed. In many glomeruli there were thickening and fibrinoid necrosis of the basement membranes, associated with necrosis of endothelial and epithelial cells and the presence of small numbers of polymorphonuclear cells. There was an exuberant proliferation of the epithelial cells lining Bowman's capsule, which had led to the production of large crescents. The tubules revealed extensive degenerative changes, necrosis and sloughing of the epithelial cells. Frozen sections stained for fat revealed small amounts of lipid in some of the epithelial cells. There was edema of the interstitial tissue, and numerous lymphocytes and plasma cells and an occasional polymorphonuclear leukocyte were present. A number of afferent arterioles and occasionally a larger arteriole revealed fibrinoid necrosis of the wall with a periarterial exudate, consisting largely of polymorphonuclear cells and a few lymphocytes (fig. 1 *b*).

The following anatomic diagnoses were made: subacute glomerulonephritis with hypertrophy of the kidneys (actual weight 710 Gm., normal 275 Gm.) with uremia (clinical); hypertrophy of the heart (actual weight 400 Gm., normal 345 Gm.) (hypertension); acute valvulitis (fibrinoid degeneration) of the mitral valve; focal fibrinoid degeneration of connective tissue of the pancreas, and necrotizing renal arteriolitis.

Case 2.—A housewife aged 37 years registered at the clinic Feb. 23, 1944 and was hospitalized four days later. The present illness began in October 1943, when she began to have migratory pains and stiffness of the hands, wrists, knees and ankles that lasted for a few hours to several days. In November slight swelling of the joints was noted; the patient was anemic, and she had a slight elevation of body temperature and a mild degree of dependent edema. In January 1944 edema became more marked, involving the face. Temperatures ranging to 101 F. were recorded, and her home physician observed albuminuria and pyuria. The extent of the edema fluctuated during February, but her weight increased by 7 pounds (3.2 Kg.) in the week prior to admission to the clinic. During this time she noticed pain in the left anterior portion of the thorax, with dyspnea on exertion. On several occasions she had passed watery stools.

Her physical examination at the clinic revealed normal conditions except the following: The wrist and joints of the right hand were swollen. There were a moderate degree of edema of the lower extremities and slight edema of the hands and face.

The laboratory examinations included urinalysis, which showed grade 4 albuminuria, a few erythrocytes and many leukocytes. The hemoglobin determination was 10.2 Gm. and there were 3,200,000 erythrocytes and 6,900 leukocytes; the differential count was normal. The blood urea measured 28 mg., and the urea clearance test gave normal values. The value for total serum protein was 3.3 Gm.,

with 1.5 Gm. of albumin per hundred cubic centimeters. The plasma cholesterol was elevated to 327 mg., and the total plasma lipids to 987 mg. per hundred cubic centimeters.

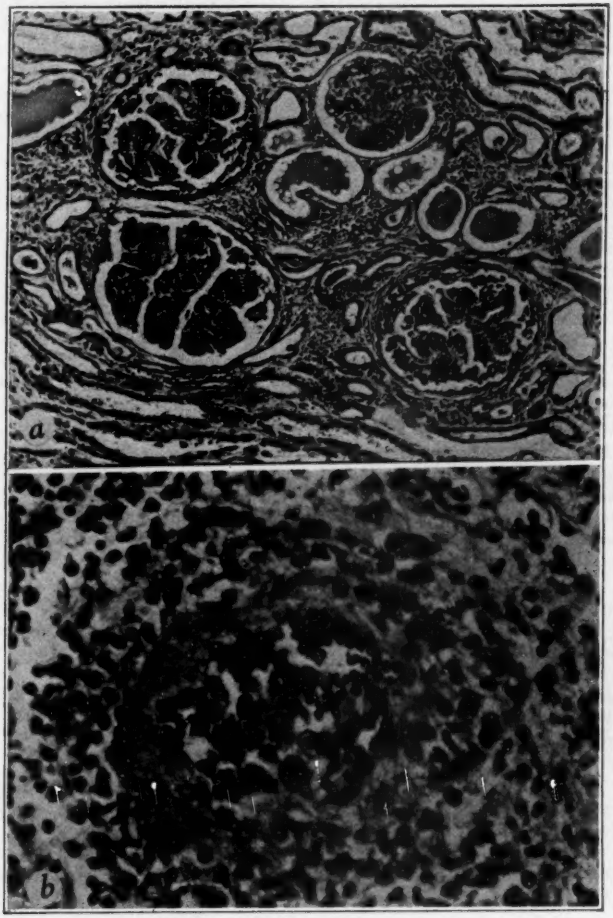

Fig. 1 (case 1).—Kidney. (*a*) Diffuse glomerulitis, crescent formation and hyaline thrombi in the capillaries; Hematoxylin and eosin; × 90. (*b*) Acute arteritis. Hematoxylin and eosin; × 435.

The patient's stay in the hospital lasted twenty-four days, and her course was quite satisfactory. Within a week she was edema free. All symptoms and findings referable to her joints completely disappeared, and no adequate explanation of

their cause could be given. Her temperature exceeded 99 F. on only one occasion. The hemoglobin determination rose to 15 Gm. and the erythrocyte count to 4,520,000 after three transfusions totaling 1,500 cc. of whole blood.

After returning home on March 21, the patient felt well. However, on April 6, she had a chill and elevation of temperature to 102.5 F. The following day her wrists and the joints of her hands became painful and swollen. Later the periodic diarrhea and pain in the left anterior thoracic region occurred.

The second admission was on April 18, 1944. The patient's temperature was 102 F. and the pulse rate 100 beats per minute. Several erythematous macules and plaques were scattered over her face, trunk and thighs, and the joints of the fingers were swollen. A moderate degree of edema was present. Urinalyses revealed albuminuria, hematuria and pyuria as before. The hemoglobin level was 10 Gm., and repeated leukocyte counts varied from 5,200 to 13,400. The blood urea determination was then 56 mg. and the serum sulfate 10.8 mg. per hundred cubic centimeters. The serum protein level was 4.2 Gm., and the value for total lipids was 1,005 mg. per hundred cubic centimeters of plasma.

During the next month the patient's course was steadily downhill. She showed a moderate febrile reaction and a gradually increasing degree of renal failure. Pericardial friction rubs and a mitral diastolic murmur developed. There were electrocardiographic changes compatible with pericarditis. The lesions of the skin faded somewhat and were not thought to be typical of disseminated lupus erythematosus. Terminally a troublesome stomatitis and proctitis developed. The patient became orthopneic, more edematous and, finally, comatose.

Necropsy.—The peritoneal cavity contained 500 cc. of cloudy fluid. The right pleural cavity contained 750 cc. of fluid and flecks of fibrin. There were fibrinous adhesions between the pericardium and the lung. The left pleural cavity contained 1,500 cc. of dark amber fluid. The pericardial sac measured 16 cm. in transverse diameter and contained 250 cc. of sanguinofibrinous exudate. Fibrinous exudate covered the visceral and parietal layers of the pericardium.

The heart weighed 336 Gm. (normal 230 Gm.). The mitral valve was thickened and edematous. There was a row of granular, pyramid-shaped vegetations along the line of closure of most of the posterior mitral leaflet and a similar but shorter row on the anterior leaflet (fig. 2 *a*). Some of these vegetations extended over the surface of the leaflet and up on the auricular wall. Similar granular but flatter vegetations were also found on the chordae tendineae. On the endocardial surface of the left ventricle, 2.0 cm. below the aortic valve, there was a flat granular mural vegetation. There were a few small vegetations on both surfaces of the tricuspid leaflet.

The pleura of the lungs contained many petechiae. There was granular fibrinous exudate on the pleural surface of the lower lobe of the right lung. Firm nodular consolidated areas could be felt in the lower lobes of both lungs.

The right kidney weighed 170 Gm., and the left weighed 194 Gm. The brain appeared grossly normal except for a few small petechiae in the left basal nuclei.

Histologic Examination: There was a thick fibrinous exudate over the pericardial surfaces. In the myocardium there were hyaline thrombi in small vessels and focal and interstitial collections of polymorphonuclear cells with necrosis of some muscle fibers (fig. 2 *b*). In sections of the mitral valve the vegetations consisted largely of fibrinopurulent exudate. There were patches of fibrinoid degeneration of the connective tissue of the leaflet with actual necrosis in some places. Large numbers of polymorphonuclear cells were present in these areas. In addition to these foci, there was an acute diffuse inflammation of the entire

leaflet. The latter was well vascularized by capillaries as well as by arteries and veins. The tricuspid valve was the seat of a similar but less extensive inflammatory process.

In sections of the kidneys no normal glomeruli could be found. The most pronounced change was an extensive increase in the number of endothelial cells in the capillaries of the glomerular tufts. This had produced very cellular tufts and

Fig. 2 (case 2).—Heart. (*a*) Vegetative (nonbacterial) endocarditis of mitral valve. (*b*) Focal collections of polymorphonuclear cells in the myocardium. Hematoxylin and eosin; × 145.

occlusion of the capillaries. Fusion and necrosis of these endothelial cells in various portions of the tuft had occurred (fig. 3). Occasionally there were hyaline thrombi in the glomerular capillaries. Adhesions of the tuft to the capsule were observed frequently. In sections stained by the Mallory-Heidenhain technic collagenization of portions of the glomerular tufts and the periglomerular zones was apparent. Slight hyaline thickening of the basement membrane of the capillaries was occasionally found. The epithelial cells lining Bowman's capsule were occasionally

hypertrophied, but no epithelial crescents were observed. Except for one focus of necrotic tubules and hemorrhage in the cortex, the tubules generally appeared normal. Frozen sections stained for fat revealed a mild degree of fatty change in the epithelial cells of the convoluted tubules. There were focal collections of lymphocytes and slight edema of the interstitial tissue.

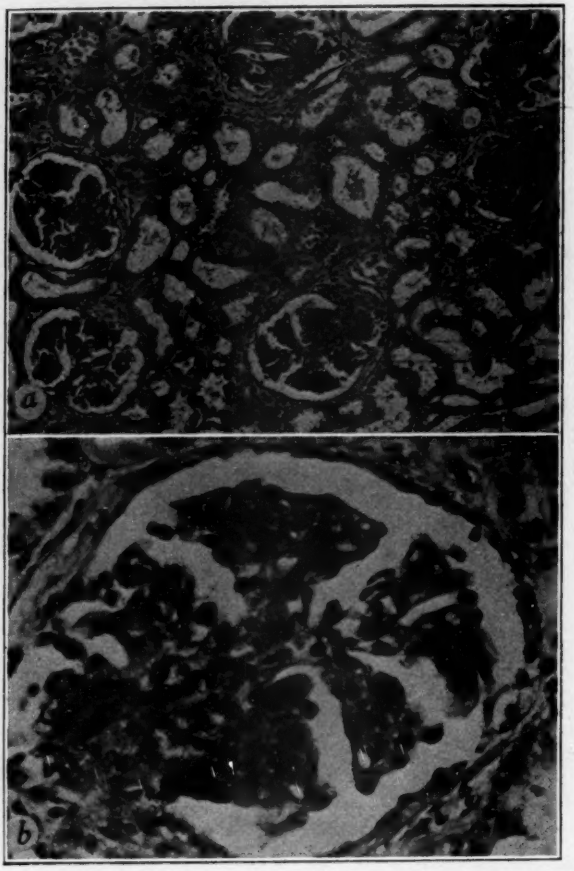

Fig. 3 (case 2).—Subacute glomerulonephritis. Proliferation of endothelial cells, fusion and focal necrosis. Hematoxylin and eosin. (*a*) × 90; (*b*) × 325.

Section of the lung revealed a fibrinopurulent pleuritis, purulent bronchitis and lobular pneumonia. In sections of the right main stem bronchus there was a bandlike area of fibrinoid degeneration and necrosis immediately beneath the epithelium.

There was severe edema of the submucosa of the colon.

The following diagnoses were made: subacute glomerulonephritis; vegetative mitral, tricuspid and mural endocarditis (nonbacterial), fibrinous pericarditis, pleuritis and peritonitis; bronchopneumonia; focal myocarditis; edema of the mucosa of the colon; hypertrophy of the heart, and petechiae of the left basal nuclei of the brain.

CASE 3.—A machinist aged 20 years first registered at the clinic on Jan. 11, 1938. He gave a history of onset of aching, stiffness and pain on motion of the joints of both hands one year previously. This lasted for six weeks. Two months prior to admission these symptoms had returned and later had involved the elbows and knees. In addition, the patient had noted an intermittent pain in the upper portion of the thorax.

Physical examination revealed a weight of 180 pounds (81.6 Kg.) and a blood pressure of 120 systolic and 80 diastolic. The pulse rate was 120 per minute and the temperature 100.8 F. Generalized lymphadenopathy was noted. The tonsils were infected. The physical examination gave otherwise essentially normal results.

The laboratory examinations included urinalysis, which showed a specific gravity of 1.029 and grade 1 albuminuria. The hemoglobin determination was 13.1 Gm., the erythrocytes numbered 4,740,000 and the leukocytes 5,600. The differential count and a special examination of a blood smear for morphologic characteristics gave normal findings. The sedimentation rate of the erythrocytes was 89 mm. in one hour by the Westergren method. A blood culture and agglutination test for Brucella gave negative results. Roentgenograms of the thorax and sinuses did not reveal any abnormality.

The patient returned Nov. 9, 1938. In February 1938, after dismissal from the clinic, a physician elsewhere had performed a tonsillectomy. Shortly afterward the patient's articular symptoms had improved, though he continued to lose weight. In the summer of 1938 he felt tired and listless. In August he had a return of joint symptoms with swelling of the hands and knees. There was transient ptosis of the right eyelid. Associated with this he had pains in the thorax and intermittent low grade fever. These symptoms persisted until the time of his readmission.

On physical examination the weight was 155 pounds (70.3 Kg.), the blood pressure 120 systolic and 80 diastolic, the pulse rate 116 and the temperature 99.2 F. An infected right tonsil tag was present. Generalized lymphadenopathy was again noted. There were slight periarticular thickening of the proximal interphalangeal joints of both hands and slight capsular swelling of both knees.

The results of laboratory studies were essentially as found on previous admission.

The patient was hospitalized for nine days. During this time there was no elevation of temperature above 99.2 F. and the pulse rate varied between 70 and 92. Slight edema of the right upper eyelid and ptosis of the lid developed. An axillary lymph node was excised for microscopic study and culture. The pathologist reported that an inflammatory reaction was present and that there was no growth of organisms on aerobic and anaerobic cultures.

The patient's third, and last, admission to the clinic was on Dec. 4, 1940. After his dismissal in November 1938 he continued to be tired and listless and was unable to gain weight but was relatively free of rheumatic manifestations until July 1940, at which time articular symptoms similar to those previously experienced recurred. About Oct. 1, 1940 the patient had an influenza-like episode characterized by generalized aching, increased malaise, thoracic pain and temperature ranging up to 101 F. From this time until readmission to the clinic he had felt too ill to work.

On physical examination the weight was 157 pounds (71.2 Kg.). The blood pressure was 126 systolic and 80 diastolic. The pulse rate was 80 and the temperature 98.6 F. Except for generalized lymphadenopathy the physical findings were essentially normal.

Urinalysis revealed a specific gravity of 1.023; albuminuria, grade 4; erythrocyturia, grade 1, and leukocyturia, grade 3. The hemoglobin determination was 9.3 Gm. The erythrocytes numbered 3,380,000 and the leukocytes 8,800. The sedimentation rate of the erythrocytes was 113 mm. in one hour. The blood urea determination was 42 mg. Blood and urine cultures showed no growth. Roentgenologic examination of the thorax showed normal conditions.

Repeated urinalyses continued to show marked albuminuria and many erythrocytes and leukocytes with a few casts. His urinary output decreased. He was hospitalized on Jan. 10, 1941, at which time slight edema of the face and lower extremities was noted. The blood pressure was 144 systolic and 98 diastolic. The value for blood urea had risen to 94 mg., and the serum sulfate level was 9.9 mg. The serum protein level was 4.3 Gm., with 2.1 Gm. of albumin and 2.2 Gm. of globulin. The serum potassium measured 34.1 mg. per hundred cubic centimeters.

His course was rapidly downhill, and, in spite of a urinary output that ranged between 900 and 1,200 cc., the blood urea mounted to a terminal level of 468 mg. There was progressive anemia, the hemoglobin level falling to 7.0 Gm. The blood cholesterol was elevated to 370 mg. and the total lipids to 1,402 mg. There was a decrease of the plasma chloride to 493 mg. and the carbon dioxide-combining power to 28.7 volumes per cent.

Terminally the patient presented the picture of uremia. He complained of irritability and fatigue. Uremic stomatitis, cough and diarrhea developed. He died March 5, 1941. Permission for postmortem examination was not obtained.

Case 4.—A foreman in the forestry service, aged 41 years, registered at the clinic on April 15, 1942 and was immediately hospitalized. He had been well until October 1941, when his right wrist became swollen, red, tender and was painful on motion. These findings persisted for three days. Thereafter there was progressive loss of strength without loss of weight. In December 1941 both ankles had become swollen, red, tender and painful on motion and there was a low grade fever. This lasted about one week. Shortly afterward he noticed edema of the feet and ankles each evening, which disappeared by morning, and that his face was slightly edematous each morning. This edema continued until the time of his admission to the clinic. Increasing dyspnea had been noted since December 1941. There was no past history of hypertension or renal disease.

On examination there was generalized pallor and a moderate degree of edema of the face and the lower half of the body. The pulse rate was 80 and the temperature normal. Repeated determinations of blood pressure averaged 144 systolic and 86 diastolic. The ocular fundi exhibited the picture of anemia with numerous petechial hemorrhages; there was no sclerosis or change of caliber of the vessels. A soft systolic apical cardiac murmur was present. The remainder of the general physical examination gave essentially normal results.

Repeated urinalyses showed a grade 4 albuminuria with a moderate number of casts, erythrocytes and leukocytes. The hemoglobin estimation was 5.1 Gm. The erythrocyte count was 1,870,000 and the leukocyte count 7,000. The blood urea determination was 178 mg. The creatinine level was 7.2 mg. The plasma chloride level was 687 mg., and the carbon dioxide-combining power was 23 volumes per cent. The serum protein level was 4.5 Gm., with 2.9 Gm. of albumin and 1.6 Gm. of globulin. The serum calcium level was 6 mg.

The patient's course in the hospital was steadily downhill. The output of urine varied between 1,000 and 2,600 cc. daily. The values for blood urea and creatinine rose slightly to 192 mg. and 8.4 mg., respectively. The physical signs of bilateral pneumonia developed, and death occurred on the eleventh hospital day.

Necropsy.—The right pleural cavity contained 800 cc. and the left 1,000 cc. of fluid. Firm, fibrous adhesions attached the apexes of the lungs to the thoracic wall. The pericardial cavity contained 100 cc. of yellow cloudy fluid. There was a thick layer of yellow fibrinous exudate over the inner surface of the pericardium.

The heart weighed 535 Gm. The surface was covered by a yellow, shaggy, fibrinous exudate which was easily dislodged.

The stomach and intestinal tract appeared normal except for the presence of six ulcers measuring 2 to 5 cm. in diameter in the ascending colon.

The right kidney weighed 165 Gm. The cut surface was pale pink, and the markings were indistinct. The cortex measured 0.5 cm. and the medulla 1.5 cm. in thickness. The left kidney weighed 195 Gm. and was similar in appearance to the right kidney.

Histologic Examination: There was a thick, fibrinopurulent exudate covering both the visceral and the parietal pericardial surface. Immediately beneath the mesothelial lining of both pericardial layers there was a zone of fibrinoid necrosis invaded by a line of polymorphonuclear leukocytes, lymphocytes and monocytes. In the deepest layers of the pericardial lining there were foci of swollen collagen undergoing fibrinoid degeneration. In these areas there were only a few associated leukocytes. In sections of the interventricular septum there were evidence of interstitial edema and small collections of polymorphonuclear cells. In the right ventricle larger collections of these cells were observed in association with foci of fibrinoid degeneration of the collagenous connective tissue.

In sections of the lower lobe of the right lung dilated bronchioles and the adjacent alveoli were filled with polymorphonuclear cells.

In sections of the colon many arterioles of the submucosa revealed acute fibrinoid necrosis of a part or occasionally of the entire circumference of the vessel wall. Fibrinoid degeneration of the collagenous connective tissue of the submucosa in the immediate vicinity of these walls and also in isolated foci was also apparent. Hyaline thrombi occluded a number of the arterioles, and there was infarction of the overlying mucosa, which was infiltrated by a purulent exudate.

In sections of the kidney no normal glomeruli could be found. Many were completely fibrotic, and in others a portion of the tuft revealed fusion and fibrosis whereas other portions revealed only an increase in the number of endothelial cells lining the capillaries. Occasionally hyaline thrombosis of the capillaries was present. Proliferation of the epithelium of Bowman's capsule with crescent formation was infrequent, but periglomerular fibrosis was common. Tubular atrophy was widespread, and many of the lining epithelial cells revealed degenerative changes, including hyaline granular degeneration. In the interstital tissue there were much fibroblastic proliferation and fibrosis but only slight edema. Numerous lymphocytes, diffusely scattered and also in focal collections, were observed. The arteriolar walls revealed mild hypertrophy of the media but no other abnormalities.

The following anatomic diagnoses were made: chronic glomerulonephritis with uremia (clinical); acute focal myocarditis; fibrinopurulent pericarditis; bronchopneumonia of the lower lobe of the right lung; hypertrophy of the heart (actual weight 535 Gm., normal 330 Gm.); silicosis of the lungs and hilar lymph nodes, and acute arteritis with infarcts and ulcers of the ascending colon.

Case 5.—A housewife aged 25 years was registered at the clinic on June 3, 1940 and admitted to the hospital three days later. Her present illness began seven

months previously, when she began to have pain, stiffness, redness and slight swelling of the elbows and knees and of the joints of her hands and feet. These symptoms were migratory in nature, with periods of remission and exacerbation lasting two to three weeks. Five months before admission urticarial erythematous lesions of the skin of the feet and ankles developed. These lesions were painless and recurred in "crops."

On physical examination her weight was 124 pounds (56.2 Kg.), the pulse rate 100 and the temperature 99.6 F. The average of repeated determinations of the blood pressure was 132 systolic and 70 diastolic. There was pallor of the mucous membranes. Except for appearing anemic, the ocular fundi were normal. There was generalized lymphadenopathy, and the spleen was palpable 4 cm. below the costal margin. A short loud apical systolic cardiac murmur was present. There was a mild degree of edema of the lower extremities. There were slight swelling and limitation of motion of the wrists, ankles, knees and metacarpophalangeal joints.

The laboratory examinations included urinalysis, which revealed a specific gravity of 1.009; albuminuria, grade 3, and the presence of a few erythrocytes and leukocytes. The hemoglobin determination was 7.0 Gm. There were 3,570,000 erythrocytes and 7,000 leukocytes. A blood smear examined for morphologic characteristics revealed only hypochromic anemia. The sedimentation rate of the erythrocytes was 133. The blood urea determination was 72 mg. The level of the total serum protein was 6.9 Gm., with 3.3 Gm. of albumin. Cultures of the urine and repeated cultures of the blood produced no growth. A roentgenogram of the thorax revealed no abnormalities. A roentgenogram of the left ankle revealed periarticular swelling.

The patient's course in the hospital was rapidly downhill. It was marked by a febrile reaction with temperature ranging to 102 F. Renal insufficiency became progressively more marked, with the blood urea reaching the level of 350 mg. A generalized "toxic" urticarial eruption was prominent. Mental confusion and subsequently the picture of an agitated mania developed. The patient died on the sixteenth hospital day. Permission for postmortem examination was not obtained. The cerebrospinal fluid obtained the day of death was essentially normal.

Case 6.—A housewife aged 33 years was registered at the clinic on March 10, 1948 and immediately hospitalized. For the past eight years she had complained of an intermittent, migratory rheumatic condition affecting the smaller joints and characterized by pain, swelling and stiffness without objective residual joint changes. In March 1947 she consulted her physician because of aching of her extremities, articular pain, urinary frequency and slight edema of the eyelids and ankles of one month's duration. She had noted progressively increasing weakness in the previous few months. The physical findings at that time revealed slight edema of the face and ankles. The blood pressure was 150 systolic and 90 diastolic, and there were no other significant physical findings. Eight months prior to admission she had been hospitalized and had been in a hospital continuously except for two periods of about a week each. Edema persisted throughout this entire time. On several occasions she had chills, fever, urinary frequency and pain in the right anterior part of the thorax. Laboratory investigations during this time included repeated urinalyses, which constantly revealed albumin, with a few casts, erythrocytes and leukocytes. The hemoglobin level varied between 55 and 64 per cent and the leukocyte count between 3,000 and 6,300. The sedimentation rate was 130 mm. in one hour. The level of blood urea nitrogen was 18 mg. and the plasma cholesterol 125 mg. The total serum proteins measured 7.3 Gm., with 2.2

Gm. of albumin. The Wassermann reaction of the blood was graded 3 plus. In August 1948 a macular eruption on her arms and trunk developed, but no changes involved the skin of her face.

On physical examination at the time of her admission to the clinic the patient weighed 156 pounds (70.8 Kg.). The blood pressure was 180 systolic and 105 diastolic. The ocular fundi were markedly anemic. The retinal arterioles were moderately narrowed and sclerosed. A few focal constrictions were present. There were cotton wool patches and retinal hemorrhages. A systolic mitral cardiac murmur was noted. There was considerable free fluid in the abdominal cavity and edema of the entire body.

The laboratory examinations included urinalysis, which revealed a specific gravity of 1.016; albuminuria, grade 4, and the presence of many erythrocytes and leukocytes. The hemoglobin determination was 5.4 Gm. per hundred cubic centimenters of blood. There were 3,160,000 erythrocytes and 9,800 leukocytes. The Kline flocculation reaction was graded 1 plus and the Kahn reaction 3 plus. The blood urea measured 118 mg.; the creatinine, 2.6 mg.; the serum sulfate, 9.3 mg., and the serum potassium, 27.3 mg. The value for total serum protein was 3.9 Gm., with 1.6 Gm. of albumin.

The patient's condition on admission was very poor. Her course was downhill, and on the evening of the fifth hospital day she became dyspneic, complained of headache and died.

Necropsy.—The peritoneal cavity contained approximately 6,000 cc. of opalescent fluid. The right pleural cavity contained 250 cc. of clear fluid, the left pleural cavity contained 2,000 cc. and the pericardial sac contained 500 cc.

The heart weighed 415 Gm. On the line of closure of the mitral valve there were a number of red, nonfriable verrucae averaging 2 by 2 mm. in diameter. The chordae tendineae appeared thin and of normal length. Beginning about 2.5 cm. proximal to the bifurcation of the aorta, there was an ulcerating membranous lesion of the intima about 5.0 cm. in length which involved the circumference of the vessel.

The right kidney weighed 260 Gm. and the left 270 Gm. The corticomedullary markings were indistinct. The cortex averaged 0.6 cm. in width and the medulla 1.7 cm.

Histologic Examination: In the myocardium, particularly in the interventricular septum, there were many arterioles that contained organized thrombi or emboli which were partially obstructing the lumen. In some of these arterioles proliferation of the endothelial cells of the intima had occurred without thrombosis. There were small collections of lymphocytes, monocytes and fibroblasts; these separated some muscle fibers and surrounded others which were necrotic. A section through a vegetation of the mitral leaflet revealed the fact that the latter consisted of a focus of swollen necrotic collagen (fibrinoid degeneration) which had elevated the endothelial surface and resulted in ulceration of the latter. Over this ulcerated area a layer of fibrin had been deposited. Aside from a slight amount of fibroblastic proliferation, there appeared to be no cellular reaction to this altered mass of collagen. In the proximal portion of the leaflet there were smaller foci of fibrinoid degeneration and edema of the collagen in association with many cardiac histiocytes (Anitschkow myocytes), lymphocytes and fibroblasts.

Sections of the ulcerating lesion of the aorta revealed fibrinoid necrosis of the walls of the vasa vasorum, with perivascular collections of lymphocytes. In the media there were foci of atrophy, degeneration and fibrosis.

In sections of the kidneys no normal glomeruli could be found. The glomeruli were large with an extensive increase in the number of endothelial cells lining the

capillaries of the glomerular tufts. Others were occluded by hyaline material, presumably thrombi (fig. 4 *a*). In many of the glomeruli the basement membranes of the epithelial cells were markedly thickened, stained intensely with eosin and had a refractile appearance. This change has been spoken of as fibrinoid

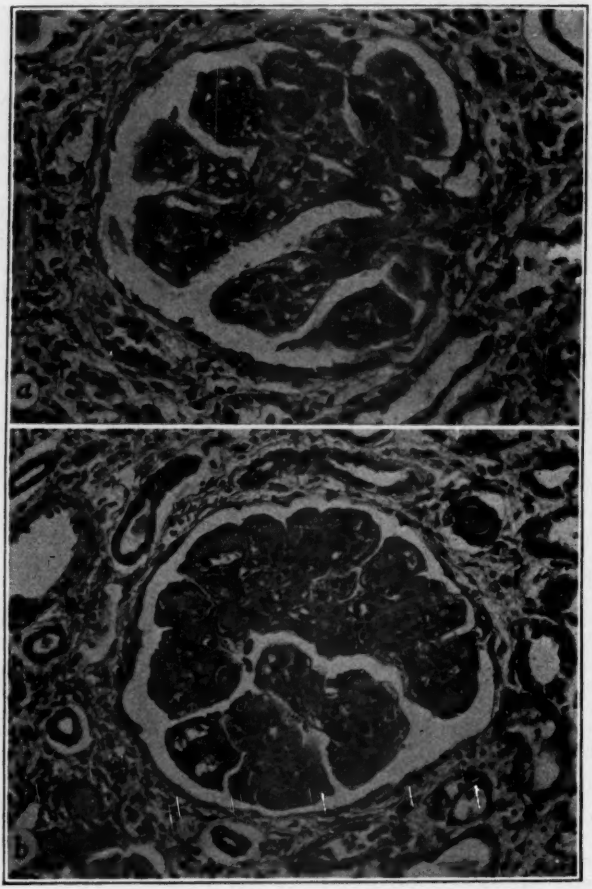

Fig. 4 (case 6).—Glomerulonephritis. (*a*) Endothelial proliferation and hyaline thrombi. Hematoxylin and eosin; × 235. (*b*) Fibrinoid degeneration of basement membranes (wire-loop). Hematoxylin and eosin; × 215.

degeneration of collagen and also as the wire-loop appearance (fig. 4 *b*). In some instances the hyaline material occluding the capillaries seemed to be derived from this thickened altered basement membrane. The thickened basement membranes

and the hyaline thrombi stained red with the Mallory-Heidenhain technic. A number of the glomerular tufts were fused to the capsule. Proliferation of the epithelial cells of Bowman's capsule had occurred in many instances but was not as extensive as in case 1.

There was marked atrophy of the tubules, which were separated widely by edema, increased interstitial connective tissue and numerous lymphocytes. Degenerative changes in the tubular epithelium were slight.

Sections of the brain revealed numerous foci of gliosis and a small infarct in the frontal lobe. Perivascular collections of lymphocytes were occasionally observed.

The following anatomic diagnoses were made: subacute glomerulonephritis with uremia (clinical); vegetative mitral valvulitis (nonbacterial); hypertrophy of the spleen (actual weight 500 Gm., normal 150 Gm.) and the lymph nodes (reticuloendothelial hyperplasia); necrotizing arteriolitis of the vasa vasorum of the aorta with medial and intimal degeneration and mural thrombi, and small infarcts and foci of gliosis in the brain.

CASE 7.—A housewife aged 26 years was registered at the clinic April 4, 1946 and admitted directly to the hospital. The patient's present complaints began in September 1945, when she noted a diffuse "drawing pain" of the posterior surface of the left thigh. The following month pain, tenderness and slight swelling of the left knee developed. Her physician made a diagnosis of "rheumatism." This persisted for about a month and then disappeared for two months. On Dec. 29, 1945 both knees, the right ankle and, a few days later, both hands and wrists became painful, tender, stiff and slightly swollen. After two months all these symptoms disappeared. Three weeks before admission she had had diffuse thoracic pains. For two weeks she had noted pitting edema of both lower extremities. Three days prior to admission edema of the face and hands developed. Her weight had increaesd 20 pounds (9.1 Kg.) in the previous month.

On physical examination her weight was 125 pounds (56.7 Kg.). The pulse rate was 90 and the temperature normal. The average of repeated determinations of the blood pressure was 165 systolic and 105 diastolic. The retinal arterioles revealed slight generalized narrowing and sclerosis with mild acute angiospastic retinopathy. A soft basilar systolic cardiac murmur was present. There were physical signs of effusion in the right pleural space. Cervical and axillary lymphadenopathy was present. There was generalized edema of the lower extremities of a moderate degree and of the face and upper extremities of a lower degree.

Urinalysis revealed a specific gravity of 1.016; albuminuria, grade 4, and the presence of a few hyaline and granular casts and many erythrocytes and leukocytes. The hemoglobin estimation was 10.2 Gm. per hundred cubic centimeters of blood. There were 4,260,000 erythrocytes and 5,900 leukocytes per cubic millimeter. The blood urea determination was 58 mg.; the creatinine, 1.2 mg.; the cholesterol, 453 mg., and the total lipids, 1,337 mg. The level of total serum protein was 3.8 Gm., with 2.3 Gm. of albumin. A roentgenogram of the thorax revealed pleural effusion on the right.

The patient's course in the hospital was unfavorable. Efforts to induce diuresis were unsuccessful, and she gained 7 pounds (3.2 Kg.). There was intermittent low grade fever, with temperature elevations ranging to 101 F. The value for blood urea increased to 156 mg. and the creatinine to 2.6 mg. The level of serum protein increased slightly, to 4.2 Gm., but the albumin fraction decreased to 2.1 Gm.

On the thirty-seventh hospital day the patient was dismissed and returned home. A communication from her physician stated that her edema and azotemia increased,

ascites developed and she died on June 8, 1946, twenty-four days after dismissal. Postmortem examination was not performed.

CLINICAL OBSERVATIONS

Of the patients 3 were male and 4 were female. The ages varied from 17 to 41 years. Three patients were of Jewish extraction. A summary of the clinical observations is presented in table 2.

In all cases there were definite but mild symptoms of an atypical arthritis. In each instance except 1 there was the objective finding of swelling. In addition, in 2 of the cases redness was noted. No history of any antecedent infection was obtained. This arthritis was the first

TABLE 2.—*Clinical Data*

					Late Edema					
Case	Sex	Age, Yr.	Duration, Mo.	"Rheumatic"* Manifestations	Grade†	Duration, Mo.	Blood Pressure, Average	Retinitis†	Temperature†	Skin Lesions‡
1	M	17	14	Stiffness, tenderness	2	2½	170/100	0	0	None
2	F	37	4	Stiffness, swelling, pain	2	3½	125/75	0	2	Erythematous macules of face, trunk and thighs
3	M	23	48	Stiffness, pain, aching, swelling	2	2	144/98	0	2	None
4	M	41	6½	Tenderness, pain, redness, swelling	2	4	144/86	Present	1	None
5	F	25	7	Stiffness, pain, redness, swelling	1	?	132/70	0	2	"Urticarial" lesions of feet and ankles
6	F	33	96	Stiffness, pain, swelling	3	10	180/105	Present	1	Macular eruption of arms and trunk
7	F	26	6	Tenderness, pain, swelling	2	½	165/105	Present	1	None

* "Rheumatic" includes arthritic and periarticular changes.
† On the basis of 1 to 4 (0 means normal or absent).
‡ No patient showed skin lesions "typical" of lupus erythematosus.

symptom to develop and persisted for widely variable periods before the onset of severe renal dysfunction. It was migratory in nature and appeared to leave no residua. Even in cases 2 and 3, in which most careful studies were made by members of the section concerned with rheumatic diseases, no definite diagnosis could be established. The cause of the thoracic pain noted in cases 2, 3 and 7 is not known. The finding of pleural effusion in all necropsy cases suggested pleuritis as an etiologic factor.

The first evidence of severe renal derangement was the presence of moderate albuminuria, hematuria and pyuria. As this progressed, the albuminuria became more marked and the patient entered the striking phase of the disease, namely, the phase of nephrotic edema. This was characterized by more or less massive edema, decreased levels of serum

protein with a particular decrease in the albumin fraction and an elevation of the values for plasma cholesterol and total lipids. Urinary output was generally decreased, and attempts to control or decrease the edema were usually unsuccessful. Once definite retention of nitrogen developed, the course was rapidly downhill and rather promptly terminated fatally. It should be pointed out that this is at variance with the usual course of patients suffering from chronic glomerulonephritis with the nephrotic syndrome. Further, it is not the picture of the mild renal complications usually described in the classic cases of lupus erythematosus.

Only in case 2 was there a heart murmur definitely diagnostic of endocarditis. This was a mitral diastolic murmur occurring in the patient who also had a recurrent pericardial friction rub. In 5 other cases apical systolic murmurs were present but were not considered diagnostic of any specific lesion. It should be noted that moderate to severe anemia was present in all cases.

The occurrence of ptosis of the eyelid in case 3 is of interest and probably not without significance, in view of the description by Libman [7] of a patient who had such a sign associated with fever, arthralgia, pleurisy and pericarditis. In that patient lupus erythematosus subsequently developed a week prior to death. The occurrence of ptosis of the eyelid in this instance is taken to indicate involvement of the central nervous system. In case 2 petechial hemorrhages were found in the left basal nuclei at necropsy. In case 5 there was also indication of a disturbance of the central nervous system as evidenced by the development of mental confusion and agitated mania. The latter was not considered to be part of the picture of uremia. In case 6 the diffuse areas of gliosis with infarction of an area of the frontal lobe of the brain demonstrates that the disease may affect the nervous system in a widespread fashion. There still remains a need for further investigative work on this phase of this complex disease.

LABORATORY OBSERVATIONS

Pronounced albuminuria on repeated determinations was a constant finding in the later stages of the disease. In those cases in which the total protein excreted in a twenty-four hour specimen was determined, the values ranged from 1.6 to 25 Gm. There was considerable variation from day to day in the same patient. All patients showed a mild to moderate degree of hematuria and generally a few to moderate number of tubular casts.

Moderate to severe secondary anemia was a constant finding late in the course of the disease. While the renal insufficiency undoubtedly

7. Libman, E.: Some Aspects of "Libman-Sacks Disease," J. Mt. Sinai Hosp. 9:621-629 (Nov.-Dec.) 1942.

was a contributory factor, it was probably not the only one. In cases 2 and 3 secondary anemia was present prior to the development of renal insufficiency. Leukopenia on at least one occasion was observed in 3 of the 7 cases.

Marked reduction in the level of serum protein was present in all cases except case 5. In all cases there was a reduction of the albumin fraction, and in 5 of the 7 cases there was reversal of the normal ratio of albumin to globulin. Whether these aberrations were the result of the renal lesion exclusively or whether they represented a disturbance elsewhere in the body is not known.

The values recorded in table 1 for serum sulfate were usually those found on admission, although in cases 2 and 5 the determination was made later in the course of the patient's hospitalization. The levels of serum potassium, on the other hand, were all made in the terminal phases of the disease. It is of interest that the levels were practically normal in 3 cases and markedly elevated in 3 cases.

PATHOLOGY

Gross examination at necropsy revealed large, pale kidneys with scattered petechial hemorrhages in all cases. From the histopathologic point of view the most important lesions were those in the kidneys. In all these cases the diagnosis of glomerulonephritis was unquestionable. The fact, however, that the usual histologic lesions of this disease were associated with other lesions in the kidneys and in other organs that are not usually associated with glomerulonephritis is worthy of comment (table 3).

In the kidneys the occurrence of fresh hyaline thrombi in the glomerular capillaries in cases 4 and 6 and focal fibrous lesions of the glomerular tufts in cases 2 and 4 was suggestive of the renal lesions which occur in subacute bacterial endocarditis as described by Loehlein,[8] Baehr[9] and Bell.[10] Identical lesions, however, have also been described by Bell in cases of subacute glomerulonephritis, without any evidence of endocarditis. The hyaline thrombi which occur in subacute bacterial endocarditis have been interpreted by him as the result of the action of bacteria and their toxic products. Their origin in our cases is also difficult to explain, since blood cultures gave persistently negative results. The focal fibrous lesions in subacute bacterial endocarditis have been attributed by Bell to proliferation of the capillary basement

8. Loehlein, M.: Ueber hämorrhagische Nierenaffektionen bei chronischer ulzeröser Endokarditis (embolische nichteiterige Herdnephritis), Med. Klin. **6**: 375-379 (March 6) 1910.

9. Baehr, G.: The Significance of the Embolic Glomerular Lesions of Subacute Streptococcus Endocarditis, Arch. Int. Med. **27**:262-264 (Feb.) 1921.

10. Bell, E. T.: Renal Diseases, Philadelphia, Lea & Febiger, 1946.

membranes. In our opinion these fibrous lesions are simply the end results of endothelial proliferation, injury and fusion of segments of the glomerular tufts. That endothelial cells have the inherent ability to function as fibroblasts has been well demonstrated by Maximow and Bloom.[11]

Of singular interest because of certain clinical aspects of these cases was the occurrence of well developed thickening and fibrinoid necrosis of the capillary basement membranes (wire-loop lesion) in 2 of the cases (cases 1 and 6). This lesion has been considered as characteristic of lupus erythematosus by Klemperer, Pollack and Baehr.[6] It was present in 12 of their 20 cases of disseminated lupus erythematosus. Stickney and Keith[12] found this lesion in 5 of 15 cases, and Bell[10]

TABLE 3.—*Pathologic Manifestations*

	Kidneys				Heart					
Case	Weight, Gm.*	Glomerulitis	Wire-Loop Changes	Crescents	Weight, Gm.*	Valvulitis	Pericarditis	Myocarditis	Arteritis	Comment
1	710 (275)	Severe	Moderate	Many	400 (345)	Mitral	None	None	Renal	Ascites and hydrothorax; fibrinoid degeneration of connective tissue of pancreas
2	364 (290)	Severe	Slight	None	336 (290)	Mitral, tricuspid	Severe	Moderate	None	Fibrinous pleuritis and peritonitis; bronchopneumonia; hydrothorax
4	360 (290)	Severe	None	Few	535 (330)	None	Severe	Moderate	Intestinal	Bronchopneumonia; infarcts and ulcers of colon; hydrothorax
6	530 (303)	Severe	Moderate	Few	415 (282)	Mitral	None	Moderate	Vasa vasorum of aorta	Ascites and hydrothorax; hypertrophy of spleen and lymph nodes (reticuloendothelial hyperplasia)

* Numbers in parentheses represent normal weights.

found it in 11 of 21 cases, but it was pronounced in only 6 instances. Thickening of the capillary basement membranes of the glomeruli is observed in many other diseases, such as hypertension,[10] lipid nephrosis,[10] eclampsia,[13] subacute glomerulonephritis[10] and subacute bacterial endocarditis.[14] Actual necrosis of the thickened basement membranes as indicated by the fact that the membrane stains red with azocarmine rather than the customary blue has also been observed by one of us and Bell[10] in subacute bacterial endocarditis and in subacute

11. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

12. Stickney, J. M., and Keith, N. M.: Renal Involvement in Disseminated Lupus Erythematosus, Arch. Int Med. **66**:643-660 (Sept.) 1940.

13. Dexter, L.; Weiss, S., and others: Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, Little, Brown & Company, 1941. Bell.[10]

14. Christian, H. A.: The Kidneys in Subacute Streptococcus Viridans Endocarditis, J. Mt. Sinai Hosp. **8**:427-440 (Jan.-Feb.) 1942. Bell.[10]

glomerulonephritis without endocarditis.[14] The patients with wire-loop lesions in this report had evidence of valvulitis and verrucae, but the results of blood cultures were always negative.

Although a good case can be made against the specificity of the wire-loop lesion, its importance in the interpretation of these cases is accentuated by the occurrence of foci of fibrinoid degeneration of collagen in the heart (cases 1, 2 and 6); in the connective tissue of the pancreas (case 1) and bronchi (case 2), and in arterioles of the kidney (case 1), in the colon (case 4) and in the aorta (case 6).

The valvular lesions resembled those of rheumatic fever in that there was considerable fibrinoid degeneration of the connective tissue of the leaflets. The occurrence of numerous polymorphonuclear leukocytes in association with the foci of fibrinoid degeneration was more like that observed in subacute bacterial endocarditis, but no bacteria could be found. The presence of numerous polymorphonuclear leukocytes in the myocardial and pericardial lesions also resembled corresponding lesions of subacute bacterial endocarditis, and Aschoff bodies were not observed. Aside from the fact that the exudative phase of the tissue reaction was more pronounced than usual, the histologic appearance of the cardiac lesions was consistent with that frequently observed in disseminated lupus erythematosus and so-called Libman-Sacks[5] disease. Finally, the myocardial lesions were different from those described by Gouley[15] in uremia or from those observed by Gore and Saphir[16] in glomerulonephritis.

The necrotizing arteriolitis which was noted in the arterioles of the kidney, colon and aorta has also been described in cases of disseminated lupus erythematosus, acute and subacute bacterial endocarditis and acute rheumatic fever. The lesions are identical with those observed in primary arteritis (periarteritis nodosa), but the predominance of the glomerulonephritis and the small number of arteries involved in these cases are enough to exclude the diagnosis.

GENERAL COMMENT

Although endocarditis was present in 3 of the 4 cases in which necropsy was done, in no instance did this seem to play a prominent part in the clinical picture. The results of blood cultures were all negative in the 6 cases in which this examination was made.

Stickney and Keith[12] described in detail the clinical and pathologic findings in the renal lesions in 15 cases of disseminated lupus erythem-

15. Gouley, B. A.: The Myocardial Degeneration Associated with Uremia in Advanced Hypertensive Disease and Chronic Glomerular Nephritis, Am. J. M. Sc. **200**:39-49 (July) 1940.

16. Gore, I., and Saphir, O.: Myocarditis Associated with Acute and Subacute Glomerulonephritis, Am. Heart J. **36**:390-402 (Sept.) 1948.

atosus in which necropsy was done at the Mayo Clinic. From the clinical standpoint the renal lesions in our group of cases bear little similarity to those of Stickney and Keith, which showed no instance of the nephrotic syndrome.

Study of the records of the cases reported offers no clue regarding any specific therapeutic measure other than general supportive treatment. Recognition of the syndrome may be of value in determining prognosis. In our hands it has made an accurate prognosis possible on several occasions in spite of the fact that the patient's clinical condition appeared relatively good, or even improving, at the time.

Although it is apparent from what has been said regarding pathology observations that many of the lesions observed in these cases were identical in appearance with those observed in classic disseminated lupus erythematosus, it is necessary to point out that the renal disease was the primary condition responsible for the patient's death. This renal disease was a glomerulonephritis. The basic lesion in this type of glomerulonephritis was proliferation of the endothelial cells of the capillaries leading to obstruction of the capillary loops. In many of the glomeruli the proliferation of endothelial cells was followed by fusion and necrosis and in some instances by fibrosis and hyalinization. These lesions were accompanied with proliferation of epithelial cells of the capsule (crescent formation) and in 2 cases by fibrinoid necrosis of the basement membranes (wire-loop change). The latter lesion, however, was focal in distribution and not extensive enough to produce the signs of renal insufficiency present in 3 cases. The latter was the result of endothelial proliferation and occlusion of capillary circulation—a diffuse glomerulonephritis.

The term "diffuse collagen disease" has been used by some workers to denote the morphologic basis of disseminated lupus erythematosus. The valid objections to this term have been assembled and well expressed by Duff [17] and need not be repeated here. For those who would like to consider the cases which are the basis of this report as examples of diffuse collagen disease it should suffice to point out that the fundamental lesions were in the kidneys and involved first and foremost not the collagenous elements but the endothelial cells of the glomerular capillaries.

It may be significant that the four diseases which have received greatest consideration in the morphologic differential diagnosis are glomerulonephritis, disseminated lupus erythematosus, rheumatic fever and periarteritis nodosa. The lesions found in these diseases have all been interpreted in recent years as manifestations of antigen-antibody reactions. In the case of glomerulonephritis, rheumatic fever and peri-

17. Duff, G. L.: The Diffuse Collagen Diseases: A Morphological Correlation, Canad. M. A. J. **58**:317-325 (April) 1948.

arteritis nodosa the reproduction of the corresponding lesions in animals is dependent on the production of hypersensitivity. For this reason some workers consider these conditions as "hyperergic" (allergic) diseases and postulate a similar pathogenesis for all of them. However, as Duff [17] and Klemperer and co-workers [6] have indicated, one cannot accept such conclusions on the basis of morphologic evidences alone.

An interesting recent observation in this group of diseases has been the description by Hargraves [18] of a cell he has designated the "L. E. cell." He has observed this cell in special preparations of bone marrow from patients suffering from acute disseminated lupus erythematosus with and without the typical lesions of the skin. Subsequently, this cell was observed in preparations of the marrow of patients suffering from conditions other than acute disseminated lupus erythematosus, when the marrow was mixed with the plasma of patients suffering from acute disseminated lupus erythematosus. Most recently the cell has been observed in normal peripheral blood that has been incubated for a short time with the plasma of patients suffering from acute lupus erythematosus. The production of the characteristic cell appears to be dependent on nucleolysis, phagocytosis and agglutination. It further suggests, as do certain alterations in serologic reactions, that hypersensitivity plays an important role in the disease process. It is hoped that this phenomenon will constitute a useful tool with which to secure added information regarding this group of diseases.

SUMMARY

Following the description by Libman and Sacks [5] of a diffuse disease that was characterized by verrucous endocarditis and that might or might not be accompanied with the certain dermatologic manifestations known as lupus erythematosus, considerable interest in the disease developed. With it there developed confusion as to what constituted the disease and the conception that verrucous endocarditis was a necessary feature. Later Libman [19] pointed out that this concept was fallacious and further that the endocarditis itself was not responsible for the clinical picture. He stated, "We have here a generalized disease in which there may be the endocardial vegetations alone, the lupus erythematosus alone, both conditions or neither." Certainly, as Keil [20] stated,

18. Hargraves, M. M.: Presentation of Two Bone Marrow Elements: The "Tart" Cell and the "L.E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25-28 (Jan. 21) 1948.

19. Libman, E.: The Varieties of Endocarditis and Their Clinical Significance, Tr. A. Am. Physicians **53**:345-351, 1938.

20. Keil, H.: Conception of Lupus Erythematosus and Its Morphologic Variants with Particular Reference to "Systemic" Lupus Erythematosus, Arch. Dermat. & Syph. **36**:729-757 (Oct.) 1937.

"The integument can no longer be regarded as the principal locus of the disease, particularly in the acute phase."

If one follows the suggestion of Gross,[21] later advocated by Libman,[7] of designating all these as cases of Libman-Sacks disease, leaving lupus erythematosus as the designation of the characteristic lesion of the skin, one has a general term for a diffuse disease which has been shown to have certain common clinical and pathologic manifestations. This plan would seem to recommend itself for several rather obvious reasons. In the first place it is a nondescriptive term which may be dropped as soon as the cause for the disease is determined and a name based on cause can be substituted. Secondly, the term "lupus erythematosus" implies primarily a disease of the skin, which it almost certainly is not. Thirdly, there is no good evidence of any relation between this disease and tuberculosis, thus making the term "lupus" misleading. Finally, it obviates the necessity of using the ambiguous, incomprehensible term "lupus erythematosus sine lupo."

In conclusion, we believe that the cases herein reported represent a group in which the underlying pathologic features are similar to those in cases classified as instances of Libman-Sacks disease or, more commonly as, "lupus erythematosus." The syndrome is characterized by arthritic and periarthritic manifestations, followed by a diffuse generalized disease in which a glomerulonephritis with the nephrotic syndrome is the central theme. In all instances of the syndrome observed, the outcome has been rapidly fatal once the nephrotic picture becomes manifest. The pathologic and bacteriologic studies failed to reveal a specific bacterial or viral agent. These findings suggest, but do not permit the conclusion, that a hyperergic state may be an important factor in the Libman-Sacks syndrome.

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21. Gross, L.: The Cardiac Lesions in Libman-Sacks Disease with a Consideration of Its Relationship to Acute Diffuse Lupus Erythematosus, Am. J. Path. **16**:375-407 (July) 1940.

MIXED MENINGITIS

A Case of Combined Pneumococcus and Klebsiella Meningitis with Recovery

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THIS CASE of mixed meningitis due to Diplococcus pneumoniae and Klebsiella pneumoniae (Friedländer's bacillus) is reported because a search of the medical literature has failed to reveal a prior case of this combination.

Mixed meningitis of metastatic or hematogenous origin is apparently a rare condition, as there have been relatively few such cases reported in the literature. Cases of mixed meningitis in which the infection entered by direct extension from the middle ear, the mastoid or the paranasal sinuses or from cranial trauma have been reported more frequently. Even the latter cases have been few, however, when considered in relation to the thousands of cases of meningitis of all types that have been recorded. This is somewhat surprising: One would think that where the meninges are contaminated by direct extension a mixed infection would be the rule rather than the exception, but such is not the case. For instance, in a series of 58 cases of otorhinogenic meningitis reported by Burman, Rosenbluth and Burman,[1] not a single mixed infection was described. In the vast majority of recorded cases the meningitis has been caused by single organisms, although these have been of infinite variety, including bacteria, protozoa, fungi, helminths and others.

While pneumococcic meningitis is not uncommon, meningitis due to Klebsiella pneumoniae alone or in combination with other organisms is rare. Jacob and Top[2] recently assembled 33 cases of klebsiella meningitis from the literature, to which they added 7 cases of their own. Of their 7 cases, the spinal fluid culture in 1 showed unidentified gram-positive bacilli, and in another, unidentified gram-positive cocci in addition to Friedländer's bacilli. It was stated that the probable primary focus was the middle ear, the mastoid or the sinuses in over 50 per

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1. Burman, H. J.; Rosenbluth, M., and Burman, D.: Otorhinogenic Meningitis: Report of 58 Cases, Arch. Otolaryng. **35**:687-719 (May) 1942.

2. Jacob, S. S., and Top, F. H.: Friedländer Bacillus Meningitis: Report of 7 Cases with 2 Recoveries, Ann. Int. Med. **28**:1003-1009, 1948.

cent of the 40 cases studied. After Jacob and Top's article was published, Schloss, Davidson and Hilton [3] described an interesting case of pneumococcic meningitis which followed the plastic repair of a posttraumatic naso-orbital fistula. Several months after this infection had been cleared with intrathecal and intramuscular injections of penicillin and intravenous injections of sulfadiazine, klebsiella meningitis developed. Complete recovery from the latter was achieved with intrathecal and intramuscular use of streptomycin after penicillin and sulfadiazine had been employed without apparent benefit. With the addition of our case to this list, 42 cases of klebsiella meningitis have been reported to date.

Among the cases of mixed meningitis reported in recent decades were 6 listed by Neal [4]: 1 of meningococcus-staphylococcus meningitis; 1 of meningococcus–Salmonella paratyphi meningitis; 1 of streptococcus-staphylococcus meningitis; 1 of streptococcus-pneumococcus-staphylococcus meningitis; 1 with streptococci and staphylococci combined with an unidentified coccus, and 1 with six organisms, only one of which was identified. No information was given as to the origin or the outcome of these infections. Cases of mixed meningococcic and tuberculous meningitis were recorded by Zanini,[5] Cislaghi,[6] Lemieux, Morin and Nadeau [7] and others. Five cases were reported by Ashmun [8] in which pneumococci, streptococci and Diplococcus catarrhalis were found in various combinations. Moritz [9] reported tubercle bacillus-klebsiella meningitis; Baldor,[10] streptococcus-staphylococcus meningitis; Gaffney,[11] pneumococcus–Hemophilus influenzae meningitis; Guthrie and Anderson,[12] meningococcus–Salmonella enteritidis

3. Schloss, E. M.; Davidson, J. H., and Hilton, K. C.: Klebsiella Meningitis: A Case Cured with Streptomycin, Ann. Int. Med. **29**:540-544, 1948.

4. Neal, J. B.: Meningitis: Distribution According to Age and Etiology, J. A. M. A. **82**:1429-1430 (May 3) 1924.

5. Zanini, A.: Mixed Meningococcic-Tuberculous Meningitis in a Child: Case, Riv. di pat. e clin. d. tuberc. **19**:152-158, 1946.

6. Cislaghi, F.: Mixed Tuberculous and Meningococcic Meningitis: Case, Pediatria **48**:585-598, 1940.

7. Lemieux, R.; Morin, E., and Nadeau, H.: Combined Tuberculous and Meningococcic Infection: Case with Autopsy, Laval méd. **9**:295-307, 1944.

8. Ashmun, S. H.: Pneumococcic Meningitis Combined with Streptococcus and Diplococcus Catarrhalis, Ohio State M. J. **29**:243-246, 1933.

9. Moritz, D.: Mixed Infection of Meninges with Tubercle Bacilli and Friedländer's Bacilli, Orvosi hetil. **81**:603-604, 1937.

10. Baldor, J. F.: Nonpurulent Mixed Streptococcus and Staphylococcus Aureus Meningitis: Value of Diagnostic Mordant Serotherapy and Therapy with Sulfanilamide Derivatives, Rev. méd. cubana **51**:159-173, 1940.

11. Gaffney, J. C.: Mixed Infection of Meninges with H. Influenzae and Pneumococcus, Brit. M. J. **1**:346, 1940.

12. Guthrie, K. J., and Anderson, T.: Double Infection of Meninges with Meningococcus and Gaertner's Bacillus, Brit. M. J. **1**:193-194, 1941.

meningitis, and Roberts [13] H. influenzae–staphylococcus meningitis. Gould [14] reported a case of post-traumatic meningitis in which a pneumococcus, a streptococcus, a gram-negative bacillus, a gram-negative diplococcus and an unidentified spore were found in various combinations in the spinal fluid at different times.

Several cases of meningitis in which two organisms were found serially but not in combination were reported in addition to the one reported by Schloss and co-workers.[8] Rosenblum and Pearlman[15] described a case in which only meningococci were found in the first culture of the spinal fluid and only pneumococci were recovered in the second and subsequent cultures. The case of a patient who had meningococcic meningitis and tuberculous meningitis in sequence was reported by Todesco.[16] Brockway and Jacobs [17] recorded a case of streptococcus meningitis followed by pneumococcus meningitis. Harris, Buxbaum and Appelbaum [18] reported on 4 patients in whom Bacillus pyocyaneus infection developed during the course of intrathecal penicillin therapy for pneumococcus meningitis. Pyocyaneus infections were also encountered by Merwarth, Rosenburg and Pulito [19] in 2 patients who were receiving penicillin intrathecally for meningococcic meningitis.

REPORT OF CASE

History.—W. I. A., a 60 year old white railway mail clerk, was admitted to the hospital on the morning of March 12, 1948. Several weeks prior to this he began to complain of headaches, dizziness and intermittent pain and roaring in the ears, especially the left ear. He also began to have difficulty in maintaining his balance while walking. The patient discontinued work and remained at home, but, having always enjoyed excellent health, he felt that his illness was not serious and did not consult a physician. On March 9, 1948, he had two teeth extracted. His symptoms continued unchanged until the morning of March 12, at which time

13. Roberts, R. W.: Mixed Influenza Bacillus-Staphylococcus Meningitis Cured with Sulfonamide Therapy, North Carolina M. J. **2**:494-495, 1941.

14. Gould, A. H.: Mixed Bacterial Meningitis Following Cranio-Cerebral Trauma: Recovery from Sulfonamide Resistant Infection Following Use of Penicillin, Rocky Mountain M. J. **41**:560-561, 1944.

15. Rosenblum, J., and Pearlman, S.: Mixed Meningitis (Meningococcus and Pneumococcus): Case with Recovery, Arch. Pediat. **59**:43-49, 1942.

16. Todesco, J.: Case of Cerebro-Spinal Meningitis Followed by Tuberculous Meningitis, M. Press **207**:127, 1942.

17. Brockway, G. E., and Jacobs, M. H.: Streptococcus Viridans Meningitis Followed by Pneumococcal Meningitis in the Same Patient with Recovery, J. Pediat. **27**:273-281, 1945.

18. Harris, R. C.; Buxbaum, L., and Appelbaum, E.: Secondary Bacillus Pyocyaneus Infection in Meningitis Following Intrathecal Penicillin Therapy, J. Lab. & Clin. Med. **31**:1113-1120, 1946.

19. Merwarth, H. R.; Rosenburg, H., and Pulito, F.: Pyocyaneus Meningitis Followed by Unusual Complications Attributed to Treatment with Streptomycin, Brooklyn Hosp. J. **5**:93-96, 1947.

he complained of a severe headache centered above the left eye. He walked up and down the stairs several times and his family noticed that he was confused. Shortly afterward he became delirious and hyperactive, and restraint was difficult. The hyperirritability gradually subsided, and at the time of his entry into the hospital he was completely flaccid and unresponsive.

Physical Examination.—The patient was well developed and well nourished and had a rectal temperature of 102.6 F., a pulse rate of 110 per minute and Cheyne-Stokes respiration. The blood pressure was 140 mm. of mercury systolic and 58 mm. diastolic. The skin was cool and moist. The patient showed no response to any stimuli. The right drum membrane was retracted but smooth and glistening; the left drum membrane was retracted and slightly injected, but there was no evidence of otitis media. A general survey of the heart, lungs and abdomen revealed no evident abnormalities, and there was no lymphadenopathy.

The eyes were deviated to the left; the left pupil was larger than the right, and neither reacted to light. The fundi were normal; there was no papilledema. Nuchal rigidity was definitely not present, and the Kernig and the Babinski signs were negative. The right biceps reflex was decreased, and the patellar and achilles reflexes were decreased on the left. The abdominal and cremasteric reflexes were absent. The provisional diagnosis was cerebral vascular accident, possibly thrombosis or subarachnoid hemorrhage. The neurologic findings did not fit a localized lesion; therefore a lumbar puncture was done. The spinal fluid was found to be cream colored and viscid, and it overflowed a 600 mm. water manometer. Twenty cubic centimeters of fluid was slowly withdrawn, which reduced the pressure to 370 mm. of water.

Laboratory Data.—The specimen of spinal fluid contained 14,000 erythrocytes and 17,600 leukocytes per cubic millimeter, of which 88 per cent were neutrophils and 12 per cent were lymphocytes. The smears showed many neutrophils interspersed with gram-positive encapsulated diplococci, some intracellular, which appeared to be typical pneumococci. The sugar was decreased and the protein increased. The Kolmer and Kahn tests elicited negative reactions, and the colloidal gold curve was 2222222221. Blood studies disclosed 13 Gm. of hemoglobin per hundred cubic centimeters and 4,800,000 erythrocytes and 20,000 leukocytes per cubic millimeter, with a differential count of 95 per cent neutrophils and 5 per cent lymphocytes. The Kahn reaction of the blood was negative, the nonprotein nitrogen 40 mg. per hundred cubic centimeters and the carbon dioxide combining power was 36 volumes per cent. The urinalysis showed normal values.

Roentgenograms of the chest on the third and eighth hospital day showed minimal bronchopneumonia on the left and on the twentieth hospital day definite bronchopneumonia on the left. Roentgenograms of the sinuses showed nothing remarkable, and those of the mastoid areas revealed absence of the air cells bilaterally but showed no evidence of osteomyelitis. The electrocardiogram was normal except for sinus tachycardia.

Hospital Course.—Shortly after the patient's admission, periods of prolonged apnea necessitated the administration of oxygen intranasally and nikethamide (coramine®) intramuscularly. When the spinal fluid smear established the diagnosis of pneumococcic meningitis one hour after admission, intramuscular administration of penicillin was started with an initial dose of 300,000 units and 100,000 units every three hours thereafter. Sulfadiazine was given intravenously, 2.5 Gm. every four hours. Sufficient fluids to maintain a normal electrolyte balance and an adequate urinary output were given parenterally. Lumbar punctures were done every four hours for the purpose of gradually decreasing the spinal fluid pressure,

and 20,000 units of penicillin was instilled intrathecally every eight hours. A retention catheter was inserted; the throat was aspirated when necessary to keep the airway open and ice bags were used when the temperature exceeded 103 F.

On the second hospital day the degree of coma was decreased: It was necessary to employ local anesthesia for the lumbar punctures where none had been required before. The patient now exhibited a marked rigidity of the neck with the head fixed to the left. There was voluntary movement of the left arm and forearm, but a spastic paralysis of the right side was present. Plantar stimulation produced dorsiflexion of the great toe on the left but no response on the right. Breath sounds were absent over the lower lobe of the left lung with sibilant and crepitant rales heard above this area, and Biot's respiration was noted at times. The additional diagnosis of pneumonia of the lower lobe of the left lung was made, but it was not possible then or later to secure a sputum specimen from which to identify the type of pneumonia. The appearance of the spinal fluid was not typical of pneumococcic meningitis, and treatment was arbitrarily started with 0.3 Gm. of streptomycin intramuscularly every three hours. Hence when the first spinal fluid culture was later reported to show a mixture of Klebsiella pneumoniae and Diplococcus pneumoniae, no change in the therapy was necessary except to vary the dose of sulfadiazine to maintain a blood level of 10 to 15 mg. per hundred cubic centimeters. At the end of the second hospital day the patient's condition was still very grave.

The spinal fluid pressure returned to normal on the fourth hospital day, although the fluid remained grossly cloudy, containing 12,075 erythrocytes and 1,300 leukocytes per cubic millimeter, and the cultures showed the same two organisms. Hereafter, spinal punctures were done less frequently, being employed only as a means of following the progress of the infection and as an aid in eliminating the exudate from the spinal canal. On this day the patient was sufficiently aroused to carry on an incoherent conversation. He stated that he was blind and that the room appeared entirely dark to him. During the next seventy-two hours the patient showed no clinical response and could not be aroused. The rectal temperature fluctuated between 102 and 104 F. It was felt that an insufficient concentration of streptomycin was appearing in the spinal fluid, so beginning on the seventh day 0.1 Gm. of streptomycin was injected intrathecally every twenty-four hours for four days. The patient started to show a gradual improvement to the extent that he could be aroused at times to take nourishing liquids. Within ninety-six hours after the institution of intrathecal streptomycin therapy the patient was completely rational. On the twelfth day decubitus ulcers developed over the greater trochanters, the sacral area and the calcanei. The ulcers started as huge blebs, the largest measuring 15 cm. in diameter. These blebs soon ruptured, leaving large denuded surfaces; these were treated palliatively, and on the surface they showed improvement. At the same time herpetiform lesions appeared on the right cheek, and they remained five days.

The patient showed gradual clinical improvement, punctuated with short periods of lethargy and irrationality, from the sixteenth to the twenty-second day. On the latter day a maculopapular erythematous rash developed over the thorax and abdomen. This was thought to represent a reaction to sulfadiazine, and seventy-two hours after use of the drug was stopped the rash disappeared.

On the twenty-eighth hospital day the spinal fluid was grossly clear and microscopically cell free, and the smears and cultures were negative for pathogens. The patient was more alert mentally and was physically stronger, being able to sit on the edge of the bed for short periods. The temperature dropped to normal for the first time on the thirty-fourth hospital day, and so the use of streptomycin

was discontinued. After five days of normal temperature, the penicillin dosage was decreased to 30,000 units every three hours, and was discontinued one week later.

The patient continued to improve mentally and physically, but the temperature rose to 102 F. on the fifty-seventh day and remained there. The leukocyte count was 36,000 per cubic millimeter, with 80 per cent neutrophils and 20 per cent lymphocytes. The possibility of a brain abscess was reconsidered, but the neurologic examination again showed no localizing signs and the spinal fluid was normal. The decubitus ulcers, which had appeared to be healing satisfactorily, were probed and found to be grossly infected. Staphylococci and colon bacilli were cultured from the lesions; hence administration of penicillin, 100,000 units, and streptomycin, 0.25 Gm., every three hours intramuscularly was again started. The two large decubitus ulcers on the hips were débrided down to the greater trochanter of the femur, approximately 300 cc. of necrotic material being removed from each, and drainage was established in the lesions on the heels and over the sacrum, after which the temperature and the leukocyte count soon fell to normal. After an extended period of irrigations with a sulfathiazole-streptomycin solution the ulcers on the hips were further débrided and closed with sutures, the one on the left under general anesthesia on the seventy-ninth hospital day and the one on the right under local anesthesia on the ninety-third hospital day. The rest of the hospital stay was without incident, and the patient was released on the ninety-ninth day after a final examination of the spinal fluid, which was found to be normal.

Summarizing the therapy, the patient received 29 lumbar punctures, 53,280,000 units of penicillin intramuscularly and 340,000 units intrathecally, 68.8 Gm. of streptomycin intramuscularly and 0.4 Gm. intrathecally, 165 Gm. of sulfadiazine intravenously, 95 liters of fluids intravenously, 1,500 cc. of blood and 1,500 cc. of plasma.

Convalescent Course.—At the time of the patient's arrival at home he was able to walk with the aid of a wheeled "walker." He was placed on a schedule of daily exercises with gradually increased activity. He gained weight, and his general condition improved rapidly. The only reason for extended observation was the unsatisfactory condition of his decubitus ulcers: The one over the sacrum healed promptly and the one on the left hip, after considerable serous drainage, closed in a few weeks, but the one on the right hip broke down along the entire length of the suture line and exuded seropurulent material. Another attempt at plastic repair was considered but rejected. Since it was impossible to perform plastic repairs on the heels because of the lack of available tissue, it was decided to treat all three of the remaining ulcers conservatively. Accordingly, they were cleansed, dusted with sulfathiazole crystals and dressed at regular intervals. Under this treatment the infection subsided, and the craters filled with granulation tissue, the surface of which epithelized from the periphery inward. The latter process was complete on the hip and the left heel and nearly complete on the right heel eight months after the patient left the hospital.

At this same time a complete physical and neurologic examination was done. There was a slight amount of serous exudate in the external auditory canals and partial deafness of the left ear, with retention of bone conduction hearing. This partial deafness was worse than that known to have existed before the onset of the meningitis. There was partial blindness of the left eye and atrophy of the left optic nerve, and the pupils reacted sluggishly to light. No mental aberrations were noted. The patient's only complaints were occasional roaring in the left ear, inability to see more than light with the left eye and intermittent instability when walking, which had caused him to fall twice.

COMMENT

This case presented several unusual features in addition to the mixed infection. One was the complete absence of nuchal rigidity prior to the first lumbar puncture. It was felt that this peculiarity could best be explained on the basis that the patient was in such a deep coma due to the extremely high intracranial pressure that the muscles were in a state of flaccid paralysis and incapable of contraction. The fact that stiffness of the neck developed promptly after the lumbar puncture lowered the pressure and slightly reduced the degree of coma seemed to corroborate this view. The failure of the patient to show any sensitivity to or complications from the drugs used except a mild sulfadiazine dermatitis was fortunate, though somewhat unexpected in view of the large quantities of sulfadiazine, penicillin and streptomycin given. The decubitus ulcers appeared rather soon after the onset of the illness, and their development was not at all typical. In spite of the fact that they started as huge vesicles, they did not resemble the herpetic lesions that appeared on the face, and it was not felt that they represented the breakdown of herpes vesicles. However, there may have been a trophic factor involved in addition to the pressure factor.

The treatment of this case of meningitis corresponds, with certain exceptions, to that outlined in recent articles: There is no disagreement concerning the use of penicillin and sulfadiazine in pneumococcic meningitis [20] or the use of streptomycin and sulfadiazine in klebsiella meningitis.[21] The previous high mortality of all types of meningitis was lowered significantly with the advent of, first, the sulfonamides and, later, the antibiotics. Prior to the development of these drugs there were very few reports of recovery from pneumococcic meningitis and only 1 report of recovery from well substantiated klebsiella meningitis.[22] Regarding the use of repeated lumbar punctures and intrathecal therapy, however, there has been considerable discussion. Hayne and Brown [23] stated that these measures were not necessary in meningococcic meningitis, and Price and Hodges [20b] asserted that they were not indicated in pneumococcic meningitis. Physicians who have encountered secondary invasion of the meninges resulting from intrathecal therapy directed

20. (*a*) Barnet, G. S.: Treatment of Pneumococcal Meningitis with Sulfadiazine and Intrathecal Penicillin G with Recovery, Ann. Int. Med. **28**:642-647, 1948. (*b*) Price, A. H., and Hodges, J. H.: The Treatment of Meningitis with Penicillin Injected Intravenously and Intramuscularly, New York State J. Med. **44**:2012-2014, 1944.

21. Jacob and Top.[2] Schloss, Davidson and Hilton.[3]

22. Rothschild, K.: Meningitis Caused by Friedländer's Bacillus: Case with Recovery, J. A. M. A. **97**:1956-1959 (Dec. 26) 1931.

23. Hayne, A. L., and Brown, R. H.: Seven Hundred and Twenty-Seven Meningococcic Cases: An Analysis, Ann. Int. Med. **28**:248-259, 1948.

against the primary infection [24] are undoubtedly wary of this type of treatment. Grinker [25] and Nielsen [26] maintained that there were indications for drainage but did not advocate intrathecal therapy.

We have no particular enthusiasm for intrathecal therapy as used in this case, but because of the patient's extremely poor condition, heroic measures were deemed necessary. The procedure is relatively safe if the materials are well diluted and injected by barbotage, provided, of course, that sterile technic is employed. There were two indications for repeated lumbar punctures in this case aside from the fact that they were necessary for intrathecal therapy. First, a spinal fluid pressure of over 600 mm. of water is not conducive to longevity, and it seems logical to employ spinal taps to reduce such a pressure to a reasonable level. However, no argument would result from the possible contention that a cisternal or a ventricular puncture would be safer than a lumbar puncture for the initial release of a high pressure. It is further conceded that concentrated plasma is of value as an adjunct in reducing the pressure. Secondly, it was felt that as much as possible of the thick, heavy exudate should be removed from the spinal canal. It is believed that if this material could be prevented from organizing about vital structures some of the complications might be avoided. Slemmer [27] described a case of pneumococcic meningitis in which a localized collection of exudate had to be drained surgically. However, in his case congenital absence of part of the right frontal lobe of the brain favored such a condition.

The primary focus of infection in this case of mixed meningitis was never determined. The possibilities were ruptured brain abscess, hematogenous spread following extraction of teeth, hematogenous spread from the pneumonia and hematogenous spread or direct extension from a chronic otitis media. The neurosurgical consultants ruled out a brain abscess. The dental extraction was not considered to be an important factor, although many cases of meningitis resulting from the bacteremia following the extraction of teeth have been reported.[28] In most of these cases there were definite signs of oral infection after extraction, but there were none in this case. It was felt that the pneumonia developed after the onset of the meningitis, since there was no apparent clinical evidence of infection of the respiratory tract when

24. Harris, Buxbaum and Appelbaum.[18] Merwarth, Rosenburg and Pulito.[19]

25. Grinker, R. R.: Neurology, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1946, pp. 730-731.

26. Nielsen, J. M.: A Textbook of Clinical Neurology, ed. 2, New York, Paul B. Hoeber, Inc., 1946, pp. 371-373.

27. Slemmer, R. E.: Unpublished case.

28. Nizel, A. E., and Vibber, F. L.: Meningitis of Oral Origin: Two Cases, Am. J. Orthodontics (Oral Surg. Sect.) **28**:49-53, 1942.

the patient entered the hospital. Finally, although the ear drums did not appear entirely normal, the consulting otolaryngologist was of the opinion that the ears were not the source of the meningitis.

The elevation of temperature that persisted for twenty-six days after the spinal fluid cultures became negative was never satisfactorily explained. The use of sulfadiazine was discontinued on the twenty-second hospital day, and the antibiotics could not have been the cause for their use was not discontinued until the temperature was normal. It is possible that the presence of the decubitus ulcers was a contributing factor.

SUMMARY

A case of mixed meningitis due to Diplococcus pneumoniae and Klebsiella pneumoniae is reported because a search of the literature has failed to reveal a case of this combination. Mixed meningitis is discussed and the literature reviewed.

Recovery with minor sequelae followed treatment with sulfadiazine intravenously and penicillin and streptomycin intramuscularly and intrathecally.

This case presented several unusual features: absence of nuchal rigidity prior to the first lumbar puncture and its prompt appearance thereafter; clinical signs simulating those of a cerebral vascular accident, and persistence of an elevated temperature for thirty-three days after therapy was instituted.

The primary focus of infection responsible for this mixed meningitis was not determined, although several possibilities existed.

785 North Park Street (8).

FUNCTIONING ACINOUS CELL CARCINOMA OF THE PANCREAS ACCOMPANIED WITH WIDESPREAD FOCAL FAT NECROSIS

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EVANSTON, ILL.

SOME MALIGNANT tumors may carry on, in varying degree, the functions of the tissue from which they arise. By virtue of such behavior they produce certain symptoms and signs which facilitate their recognition. It is not generally recognized that some functioning tumors of the pancreatic acini may also give rise to a peculiar clinical syndrome which is characterized by widespread focal fat necrosis. Such a case has been observed recently at the Evanston Hospital (service of Dr. A. R. Colwell). Reports of four nearly identical cases are related to the present.

REPORT OF A CASE

A 59 year old white executive entered the Evanston Hospital, on Nov. 24, 1948, complaining of painful joints in the toes and fingers and tender nodes in the skin of the right leg. One month before admission pain and swelling appeared in the distal half of the left great toe, and two weeks later the right great toe became similarly involved. One week thereafter a large area of reddening and swelling appeared over the outer side of the right ankle, and two days prior to admission the distal joint of the right thumb became inflamed. Simultaneously two slightly tender knots (nodules) were found in the skin of the right thigh. Codeine N. F. and acetylsalicylic acid were necessary to relieve the pain in the toes, and a short course of orally administered penicillin and a triple sulfonamide mixture were of no benefit. Except for these tender parts he felt well.

Past History.—The past history included a questionable account of angina pectoris for the past three years, an appendectomy in 1914, cholecystectomy in 1927 and 2 episodes of acute pyelonephritis in 1944 and 1946 respectively. The last bout of renal infection had led to a transurethral prostatic gland resection in 1946. The tissues removed were reported as adenomatous prostatic hypertrophy.

Examination.—The patient was a healthy-looking man whose temperature was 98.0 degrees (F.); pulse rate 64 a minute, and blood pressure 146 mm. of mercury systolic and 82 mm. diastolic in the recumbent position. In the left hypochondrium there was a rounded, smooth and slightly tender mass which extended 10 cm. below the costal margin. The distal phalangeal joint of the right thumb was swollen, red and tender. The distal joints of both great toes were similarly inflamed, and behind the right external malleolus there was a 4 cm. rounded and raised swelling overlaid by dusky erythema. In the subcutaneous tissue of the inner aspect of the right thigh were two small, firm, tender and rounded nodules about 1 cm. in diameter. They were freely movable on the underlying fascia and not attached to the skin, which appeared normal.

Three successive blood counts were entirely normal except for the eosinophils numbering 7 to 11 per cent. The erythrocyte sedimentation rate ranged from 18 to 37 mm. in one hour (Westergren). The urine contained albumin (1 plus), a few hyaline casts and a few red blood cells per high power field in the centrifuged specimen. The blood nonprotein nitrogen, uric acid and total and differential serum protein levels were within normal limits. The cephalin-cholesterol flocculation and sulfobromophthalein sodium tests were not abnormal. Brucella and heterophil agglutinations were negative in all dilutions. The electrocardiogram showed minimal evidence of strain in the left side of the heart. Roentgenograms of both feet and the right thumb revealed normal bones. That of the chest showed some calcifications and apparent enlargement of the hilar nodes bilaterally and a few streaks of increased density above and parallel to the slightly elevated right side of the diaphragm. Complete roentgen ray study of the gastrointestinal tract disclosed only a few diverticula in the sigmoid colon. An excretory urogram demonstrated a normal-appearing left kidney, while the right was somewhat smaller, was irregular in outline and had minimally dilated and blunted calices. The function of both, as judged by concentration of the dye, was normal. The base of the urinary bladder contained a large rounded filling defect interpreted as an enlarged prostate gland.

Course.—After the patient rested in bed three days, the swelling in the great toes and thumb began to subside, but new nodules appeared beneath the skin of the right thigh. On November 30 two of these were removed for pathologic examination and were reported as being compatible with febrile relapsing nodular panniculitis or atypical erythema nodosum. The patient rapidly felt better and was transferred to another hospital for cystoscopic examination. This was unsuccessful, presumably because of the greatly enlarged prostate gland and, because a normal urine was found there, was pursued no further. Because the presence of a lymphoblastoma, particularly Hodgkin's disease, was suspected a therapeutic trial of roentgen ray therapy was directed to the mass in the left part of the upper part of the abdomen and to the mediastinum. The calculated depth dose to the first was 155 r and to the latter 332 r, given between December 9 and 17.

After the patient returned home new lesions continued to appear irregularly over the trunk and extremities, and on December 16 fever appeared with a chill. Every evening thereafter his temperature rose to 100 or 102 F.; anorexia, increased weakness and a 15 pound (6.8 Kg.) loss of weight ensued. He returned to the hospital on December 26, at which time his temperature was 99 F., pulse rate 72 and blood pressure unchanged. Multiple skin nodules were scattered irregularly over the entire body, with the face, scalp and genitalia excepted. A number were 5 to 6 cm. in diameter, but most ranged from 1 to 2 cm. The smaller ones were definitely in the subcutaneous fat; the overlying skin was undisturbed. The larger were bound to the skin, which was dusky red. A few were regressing with brownish pigmentation of the skin, but only one left a slight depression. A number of interphalangeal joints were swollen and painful, and the first interphalangeal joint of the right third finger, which had been the seat of an acute process earlier, showed a pale fusiform swelling, not unlike that of rheumatoid arthritis. The mass in the left hypochondrium seemed a bit larger, but it was still smooth and spleenlike.

A blood count was again within normal limits, except that the neutrophils numbered 83 per cent and the eosinophils 5 per cent. Repeated counts were similar, with percentages of eosinophils from 5 to 7. Examination of the sternal marrow revealed erythroid hyperplasia. The urine contained albumin (2 plus), many granular casts and 3 to 8 white blood cells per high power field in the centrifuged specimen. Cultures of venous blood, sternal marrow, urine and stools

revealed no pathogens. Roentgenograms of the chest and teeth were not remarkable, and comparison of the roentgenograms of the chest with roentgenograms taken in 1944 and 1946 showed the hilar changes and those in the base of the

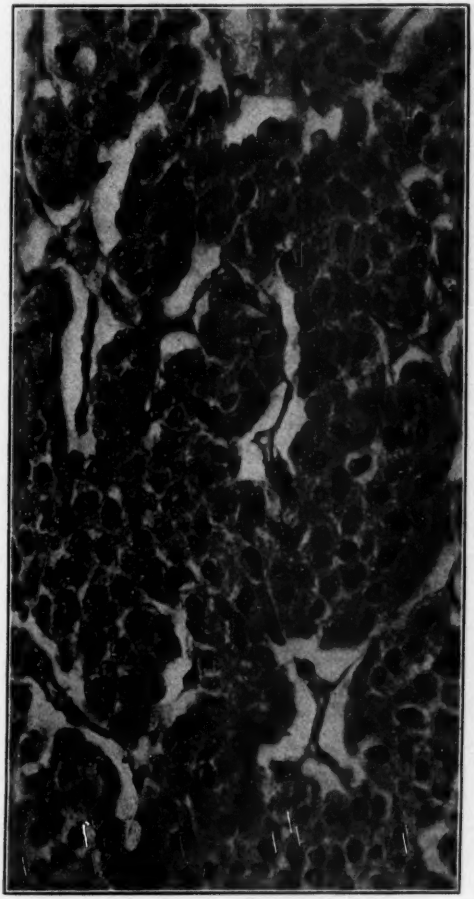

Fig. 1.—Well organized section of tumor showing well formed pseudoacini. The spaces between tumor cells and stroma are artefacts. Hematoxylin and eosin; × 300.

right lung to have been present then. Roentgen therapy had caused no change in the appearance of the pulmonary hili. Another skin lesion was examined pathologically and was found to resemble those seen earlier.

The course of the disease was not affected by 50,000 units of penicillin given every three hours for five days; 0.5 Gm. of dihydrostreptomycin every six hours for four days; and diphenhydramine hydrochloride (benadryl hydrochloride®)

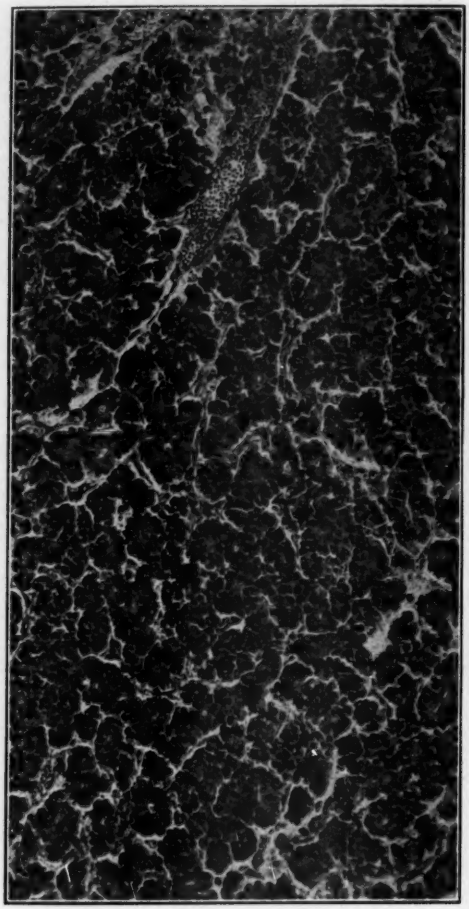

Fig. 2.—Low power photomicrograph of tumor showing resemblance to normal pancreas. Hematoxylin and eosin; × 100.

50 mg. four times daily for a week. New lesions continued to appear, and though salicylates modified the fever, the temperature continued to rise to 101 F. every evening, often followed by a drenching sweat. The patient

left the hospital on Jan. 8, 1949, and while he was at home the course was one of rapid decline. The mass in the left side of the abdomen enlarged, and a new one appeared in the midepigastrium. On February 1 thrombophlebitis appeared

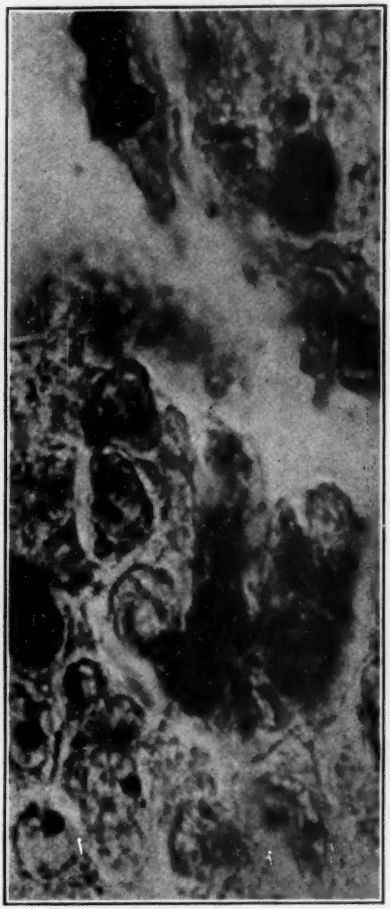

Fig. 3.—Oil immersion view of tumor cells which contain zymogen granules. Phosphotungstic acid hematoxylin; × 1200.

in both legs, and shortly thereafter extreme oliguria was noted. The patient again entered the hospital, where he died on Feb. 7, 1949.

Necropsy (performed by Dr. R. E. Lininger).—The previously noted nodules and swellings about various joints were seen. The largest measured 5 cm. and

lay in the left anterior axillary line lateral to the left nipple. As the usual incision was made, innumerable small areas of fat necrosis were noted in the subcutaneous tissue. The region of the pancreas was occupied by a large irregular mass measuring 24 by 8 by 7 cm., which extended from the convexity of the duodenum to the left posterolateral chest wall. It was attached to the midbody of the pancreas over a distance of 3 cm.; the rest of the pancreas, including its ducts, was otherwise normal. Several tumor-bearing lymph nodes were found in the falciform ligament, about the porta hepatis and celiac axis. The liver contained four large tumor nodules up to 7 cm. in diameter, and a few small peritoneal

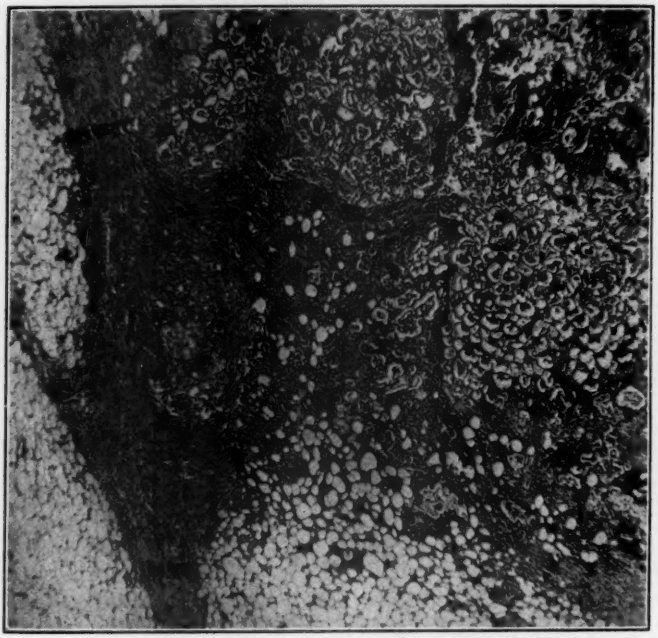

Fig. 4.—Low power illustration of an area of subcutaneous fat necrosis; × 16.

implants were found in the pelvis. Both primary tumor and hepatic metastases, when cut, showed they contained some areas of hemorrhage and necrosis; but, on the whole, the tumor was white, meaty and rather soft. A number of typical areas of fat necrosis lay in the fat adjacent to the tumor. The heart was not remarkable, and the lungs contained some basal bronchopneumonia and edema. The hilar glands showed many small calcifications. The right kidney exhibited scarring from old pyelonephritis, and the left was the seat of almost total infarction; this the result of a thrombus which occluded the renal artery just proximal to the primary bifurcation. The prostate gland was greatly enlarged by adenomatous hypertrophy, and the left iliac vein was occluded by a thrombus. The small veins

of both legs were the seat of widespread thrombosis. The brain and gastrointestinal tract were not remarkable. A sample of vertebral marrow appeared normal.

Microscopically the tumor and its metastases were composed of acidophilic polyhedral cells having large vesicular nuclei with one or two nucleoli (fig. 1). These were supported by a delicate stroma with many small vessels and in many areas closely mimicked true pancreas (fig. 2). Zymogen granules were demonstrable in many cells with phosphotungstic acid hematoxylin and with Bensley's stain (fig. 3). Ducts and centro-acinar cells were absent. The areas of fat necrosis in the skin and peritoneal fat were typical, consisting of a central area of coagulative necrosis surrounded by fat-laden macrophages, rare giant cells,

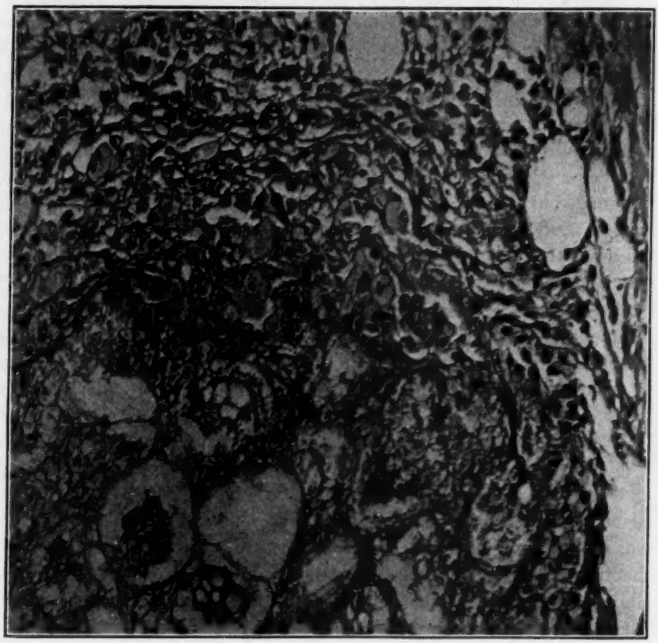

Fig. 5.—High power photomicrograph of a segment of periphery of lesion shown in illustration (fig. 4). Fat-laden macrophages border the central zone of fat necrosis. Hematoxylin and eosin; × 300.

monocytes and lymphocytes and a few neutrophils. The whole had an indolent appearance (figs. 4 and 5). A number of these lesions were sectioned serially and tumor cells were never found.

COMMENT

The correct diagnosis in this case was not made until the tumor had been examined microscopically and reports of similar ones found in the literature. For a time it was considered an atypical febrile relapsing

nodular panniculitis, but the presence of arthritis, the large abdominal mass and the rapid decline caused this diagnosis to be abandoned. It was finally agreed that the man must have a malignant growth, but this could not be correlated with the widespread fat necrosis.

A careful search of the literature revealed 4 almost identical cases.[1] The salient clinical features of these and the present case are listed in table 1, and the autopsy findings for each in table 2. The near identity of clinical and autopsy characteristics is evident.

Conclusive proof of the part played by circulating lipase is lacking in all these cases because such studies were not done. Titone mentions one urinary amylase value of 256 units in his case. Only one acinar cell carcinoma appears to have been thoroughly studied from the biochemical standpoint. This was reported by Comfort and associates.[2] Exceedingly high values for blood lipase and amylase were present and those of peritoneal fluid were even higher. They could not say positively that the tumor was functioning because it partially obstructed the duct of Wirsung, but the values for enzymes far exceeded anything ever seen in cases of duct obstruction from other causes. Apparently their patient did not exhibit fat necrosis at any site. The tumor cells contained many zymogen granules, as did those of the present case and that of Auger.[1a]

Aside from this there is other indirect evidence that the tumors in these 5 cases did produce large amounts of lipase which entered the lymphatics and blood stream and thereby caused adjacent and far distant fat necrosis. Berner [1b] thought that the fat necrosis, particularly that in the subcutaneous tissues, might be traumatic, while Hegler and Wohlwill [1c] suspected that they arose from emboli of tumor cells. They found a solitary metastasis in the right femur surrounded by fat necrosis and explained the failure to find them elsewhere on autodigestion which ensued when the surrounding tissue was rendered inviable. Titone [1d] was not sure how they came about, and Auger [1a] was the first to conclude that the enzyme alone was responsible. With 5 cases of such great similarity available for analysis it seems safe to conclude that Auger was correct. Though trauma might play some minor part in the localization of the cutaneous lesions, by permitting blood or serum to escape

1. (*a*) Auger, C.: Acinous Cell Carcinoma of the Pancreas with Extensive Fat Necrosis, Arch. Path. **43**:400 (April) 1947. (*b*) Berner, O.: Subkutane Fettgewebsnekrose, Virchows Arch. f. path. Anat. **193**:510, 1908. (*c*) Hegler, C., and Wohlwill, F.: Fettgewebsnekrosen in Subcutis und Knochenmark durch Metastasen eines Carcinoms der Pankreasschwanzes, ibid. **274**:784, 1930. (*d*) Titone, M.: Ueber ungewöhnlich ausgebreitete Fettgewebs und Gewebsnekrosen bei Pankreaskrebs, ibid. **297**:416, 1936.

2. Comfort, M. W.; Butt, H. R.; Baggenstoss, A. H.; Osterberg, A. E., and Priestly, J. T.; Acinar Cell Carcinoma of Pancreas: Report of a Case in Which Function of the Carcinomatous Cells Was Suspected, Ann. Int. Med. **19**:808, 1943.

from injured vessels, it does not explain the visceral lesions or the multiplicity of involved areas that appear as the disease progresses. If one may consider the increased hydrostatic pressure of the blood in the

TABLE 1.—*Summary of Clinical Findings*

Author	Age	Sex	Site of Initial Lesions	Site of Later Lesions	Arthritis	Roentgen Findings	Temperature	Blood Findings	Abdominal Tumor
Berner [1b] 1908.....	Old	M	Right calf	All extremities	Toes, fingers	None given	To 101 F.	None given	None; only epigastric tenderness
Hegler and Wohlwill [1c] 1930..	68	M	Lower legs	All extremities	Hands, ankles, knees, wrists	Destructive lesions of multiple bones	To 101 F.	WBC 6,500 to 12,000 3-5% Eo.	Left hypochondrium, spleenlike
Titone [1d] 1936.....	56	M	Left knee	Trunk and all extremities	Knees, elbows, hips	None given	Not given	Not given	Large nodular liver
Auger [1a] 1947.....	56	M	Heels	Trunk and all extremities	Hands, elbows	Spine and pelvis normal	To 103 F.	WBC 5,428 Eo. 8%	Hard nodular liver
Osborne 1949.....	59	M	Toes and ankle	Trunk and all extremities	Hands, feet, elbows, wrists, knees	Normal hands and feet, ribs, spine and pelvis early in illness	To 103 F.	WBC 7,000 Eo. 7-11%	Left hypochondrium, spleenlike, and midepigastrium

TABLE 2.—*Summary of Autopsy Findings*

	Primary Tumor			Sites of Fat Necrosis				
Author	Site	Size	Metastases	Skin	Joints	Abdomen	Thorax	Bone
Berner [1b]	Tail	Size of child's head	None	Yes	No mention	About tumor and pancreas	None	None found
Hegler and Wohlwill [1c]	Tail	Size of child's head	Femur	Yes	Yes	About tumor	Pleura, pericardium, lungs	Widespread
Titone [1d]	Head	Size of apple	Liver	Yes	Yes	Widespread	Pleura, pericardium	Widespread
Auger [1a]	Tail	5 cm.	Liver	Yes	Not in 1 joint examined	Widespread	Pericardium	No mention
Osborne	Body	24 × 8 × 7 cm.	Liver, regional nodes, peritoneum	Yes	Not examined	About tumor	None	None in 1 vertebral body

lower extremities as a form of trauma, this may explain the tendency to early localization there. The possibility of tumor emboli releasing lipase at distant sites is most unlikely for two reasons: First, none of these

cases had pulmonary metastases, and it seems impossible that so many emboli could have passed through the pulmonary capillary bed without setting up growth or leaving some trace of their presence; second, tumor cells have been found in only one area of fat necrosis of the great number examined. In the present case many of the lesions, when examined microscopically, still showed well preserved ghosts of fat cells. Ghosts suggestive of tumor cells were uniformly absent. The uniform presence of fat necrosis about every tumor is also good evidence that they must have produced lipase which entered adjacent lymphatics. The distribution of such lesions is similar to that seen in acute hemorrhagic pancreatitis, and it is of interest that a few cases of that disease with subcutaneous fat necrosis at far distant sites have been reported.[3] These were not instances of necrosis of subcutaneous fat in the abdominal wall which is the result of transmission via lymphatics but of localizations similar to that of the 5 cases considered here. Were it not for the great vascular damage which is an integral part of that disease, such an occurrence would undoubtedly be more common. The destruction of the pancreatic vascular bed must actually prevent the ingress of any considerable amount of enzyme to the blood stream except via the lymphatics where much is dissipated along the way. The lesions close to the tumor in these instances were identical to those in the subcutaneous tissue, suggesting a common etiology. Finally, distant fat necrosis has been produced experimentally by ligation of the pancreatic ducts or injury to the gland.[4]

The resemblance of this syndrome to febrile relapsing nodular panniculitis is an interesting one, particularly because enzyme studies seem never to have been done in the latter. Both are characterized by subcutaneous fat necrosis, and occasionally such visceral lesions appear in nodular panniculitis. Those nodules in the skin have a predisposition to affect the lower extremities, and the microscopic appearance of many seems indistinguishable from those of the present 5 cases. The resemblance, however, seems to end here. Weber-Christian disease has a reversed sex incidence; arthritis is not recorded (though arthralgia is), cutaneous lesions usually occur above the knees instead of below; the course is almost always benign with long remissions common, and some appear to have resulted from various drugs. Conversely, in some cases

3. (*a*) Chiari, H.: Ueber einen Fall von Sequestration des Pankreas nach Perforation des Magens durch Ulcera rotunda, Wien. med. Wchnschr. **26**:292, 1876. (*b*) Jenckel: Zur Pathologie und Therapie der akuten Pankreasnekrose, Deutsche Ztschr. f. Chir. **131**:253, 1914.

4. (*a*) Opie, E. L.: Disease of the Pancreas: Its Cause and Nature, ed. 2, Philadelphia, The J. B. Lippincott Company, 1910, pp. 176-199, cited by Neal, M. P., and Ellis, M. M.: Etiological Factor of Fat Necrosis, South, M. J. **23**:313, 1930. (*b*) Jenckel.[3b]

the condition seems to have been controlled by sulfonamides or penicillin. Patients examined post mortem have uniformly exhibited a normal-appearing pancreas. The possibility of temporary functional or anatomic derangement of pancreatic function must, however, be kept in mind. Certainly disturbances in biliary and pancreatic function are more common in women.

SUMMARY AND CONCLUSIONS

A case of presumably functioning acinous cell carcinoma of the pancreas is described and correlated with 4 similar ones collected from the literature.

It is believed that such tumors may, on occasion, give rise to a peculiar clinical syndrome characterized by widespread fat necrosis, arthritis, fever, a tendency to low grade eosinophilia, sometimes abdominal tumor and rapid decline.

The relationship of this syndrome to febrile relapsing nodular panniculitis (Weber-Christian disease) is discussed.

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RELATION BETWEEN NEURITIS AND THE CLINICAL BACKGROUND IN DIABETES MELLITUS

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DISORDERS of the nervous system are commonly found among a clientele of persons with diabetes. The subject having been so often dealt with since the first report, by Marchal de Calvi,[1] appeared in 1864, instead of surveying the literature I refer to exhaustive studies by Kraus,[2] Woltman and Wilder,[3] Jordan,[4] to more recent reports by Broch and Klövstad,[5] Rudy,[6] Rudy and Epstein,[7] Rundles,[8] Swartz[9] and to the pertinent chapters in Joslin's "The Treatment of Diabetes Mellitus"[10] and Wilson's "Neurology."[11] Owing to the difficulties of defining the conception of diabetic neuropathy, on the one hand, and, on the other, of establishing stable criteria from the variability of symptoms presented by the diabetic patient, much is still obscure regarding the relation obtaining between the nervous disorders and the diabetic

From the Department of Metabolic Research, Wenner-Grens Institut, Stockholms Högskola.

1. Marchal de Calvi, C. J.: Recherches sur les accidents diabétiques et essai d'une théorie générale du diabète, Paris, P. Asselin, 1864.

2. Kraus, W. M.: Involvement of the Peripheral Neurons in Diabetes Mellitus, Arch. Neurol. & Psychiat. **7**:202 (Feb.) 1922.

3. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus: Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med. **44**:576 (Oct.) 1929.

4. Jordan, W. R.: Neuritic Manifestations in Diabetes Mellitus, Arch. Int. Med. **57**:307 (Feb.) 1936.

5. Broch, O. J., and Klövstad, O.: Polyneuritis in Diabetes Mellitus, Acta med. Scandinav. **127**:514, 1947.

6. Rudy, A.: Diabetic Neuropathy, New England J. Med. **233**:684, 1945.

7. Rudy, A., and Epstein, S. H.: Review of One Hundred Cases of "Diabetic Neuropathy" Followed from One to Ten Years, J. Clin. Endocrinol. **5**:92, 1945.

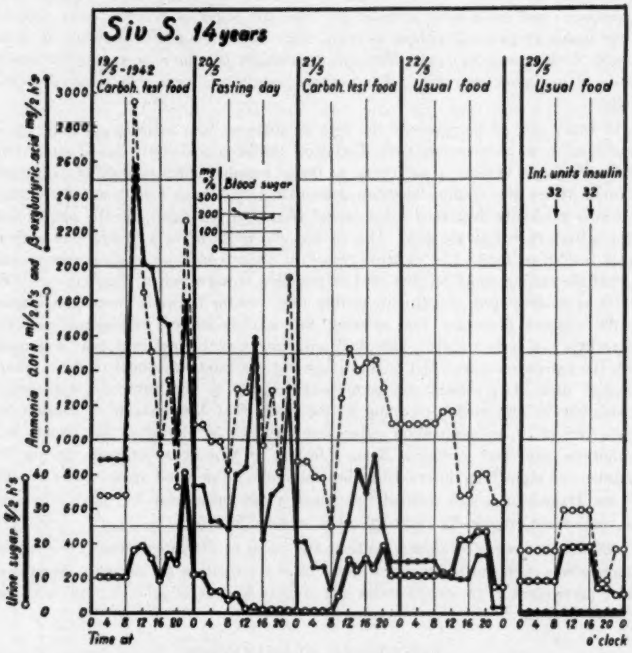
8. Rundles, R. W.: Diabetic Neuropathy: General Review with Report of 125 Cases, Medicine **24**:111, 1945.

9. Swartz, F. C.: Diabetic Neuritis, Thesis, Mayo Foundation, 1940; cited by Treusch, J. W.: Ann. West. Med. & Surg. **1**:67, 1947.

10. Joslin, E. P., and others: The Treatment of Diabetes Mellitus, ed. 8, Philadelphia, Lea & Febiger, 1946, p. 557.

11. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, London, Edward Arnold & Co., 1940, vol. 1, p. 300.

condition. In the present paper I shall endeavor to overcome these difficulties by comparing a group of diabetic patients with organic neuritis with another group of such patients without objective nervous symptoms. In each group the examination was conducted under standard conditions, the endogenous aspect of the metabolic disease being first and foremost taken into consideration.



Excretion of sugar, beta oxybutyric acid and ammonia in 1 case of grave diabetes (from Möllerström, J.: Theoretical Considerations and Practical Results in the Management of Diabetes, Acta med. Scandinav. 1947, supp. 196, p. 12).

PROCEDURE

The series of patients serving for the present investigation comprised patients hospitalized in the clinic. The fact that they were hospitalized does not indicate that their condition was particularly severe, since, as a rule, the patients under the care of the clinic were admitted from time to time for readjusting their treatment. All the patients were receiving good care, and their diabetes was well managed, most of them having been under the supervision of the clinic from the onset of their disease. The series comprised all purely diabetic patients, without any special selection, treated in the clinic during the nine month period from

January to September 1949. Patients with diabetes complicated by other chronic conditions, especially active tuberculosis, malignant tumor, pernicious anemia, those with a positive Wassermann reaction or a history of syphilis and diabetic patients with nervous complications definitely nondiabetic in origin were excluded from the present series. Every patient was subjected to routine medical and neurologic examinations. In defining the group of patients with diabetic neuritis, only objective signs were taken into account. As objective signs were regarded extinct or appreciably attenuated tendon reflexes, disturbances of sensibility within anatomically well defined areas and trophic changes arising on a neurologic basis. Patients with paresthesias and pains only, without any objective signs of neuritis, were referred to the group of patients without neuritis, since mere hypoglycemia is known occasionally to give rise to pain. Patients with slight pupillary or vegetative abnormality, if not associated with other nervous symptoms, were also referred to this group.

In every one of the patients the type of diabetes was ascertained under basic conditions, i. e., in circumstances disclosing the behavior of the blood sugar, the tendency toward ketonuria and coma, so far as possible independently of exogenous factors. When the routine medical examination had been completed, the insulin dose was gradually decreased for a period of two to five days, and the patient was given a high carbohydrate diet. This period was followed by a fasting day without either insulin or food. The patients remained under continual medical supervision, so that the testing could be abolished at the right moment when symptoms pointing to precoma developed. After the fasting day, insulin if needed was given again in the amount necessary for securing the equilibrium of metabolism and the maintenance of body weight. This final adjustment of the insulin dosage was made with the patient on a free diet qualitatively and quantitatively equal to the ordinary Swedish diet. The insulin treatment was adapted to the rhythmic, endogenous production of keto acids according to the method of Möllerström.[12] During the whole period of hospitalization urine specimens to be examined for sugar, beta oxybutyric-acid and ammonia were collected at two hour intervals during the daytime and eight hour intervals during the night. The blood sugar was estimated by the Hagedorn-Jensen method five times a day on special test days only. All the rates were graphically recorded, as is seen in the chart.

All the tests were continued, without any harm to the patient, until the evidence obtained was sufficient to provide a sound basis for treating the diabetes. In tables 1 and 2 particulars of the entire series are presented separately for patients with and without neuritis.

RESULTS OF EXAMINATION

Neurologic Changes.—Of the persons with diabetes in the present series, 74 (49.3 per cent) presented frank neuritic symptoms organic in character. Of these, 35 (47.3 per cent) were men and 39 (52.7 per cent) women. The patients ranged in age from 7 to 84 years, with averages of 49.5 (neuritic patients) and 44.1 (non-neuritic patients) years respectively. Details of the age group distribution of patients with and without neuritis are given in table 3. The outstanding feature of involvement of the nervous system is the disturbance of tendon

12. Möllerström, J.: Das Diabetesproblem, Acta med. Scandinav., 1943, supp. 147, p. 1.

TABLE 1.—*Summary of Data on Diabetic Patients with Neuritis*

Case No.	Sex	Age, Yr.	Height, Cm.	Weight, Kg.	Diabetes: Duration, Yr.	Diabetes: Insulin	Diabetes: Ketogenic Character*	Diabetes: Fasting Blood Sugar, Mg./100 Cc.† 9 A. M.	12 A. M.	2 P. M.	4 P. M.	6 P. M.	Blood Pressure‡	Albuminuria	Retinopathy	Nervous Alterations: Pupillary Refl.	Tendon Refl.	Sensibility	Paresthesias and Pains	Trophic Disturbances
1	F	37	173	67	13	96	O	260	260	200	230	220	—	+	+	+	+	+	—	+
2	M	51	172	71	3	0	B	195	184	146	139	122	+	—	+	—	+	—	+	—
3	F	59	165	75	18	48	O	...	...	...	...	...	+	+	+	—	+	—	+	—
6	F	23	156	59	15	76	O	...	...	...	...	...	—	—	—	—	—	—	—	—
8	F	54	165	83	1½	0	A	146	117	115	97	75	+	—	+	—	+	+	—	—
9	F	44	163	84	1½	32	A	271	226	218	221	223	+	—	+	—	+	—	+	—
10	F	59	157	49	17	32	O	482	503	...	372	219	—	—	+	—	+	—	+	—
12	M	36	183	77	11	72	A	...	...	...	...	...	—	—	—	—	+	+	+	+
13	F	17	160	57	9	56	O	...	...	...	...	...	—	—	—	—	+	—	—	—
15	F	32	159	68	20	72	O	...	...	...	...	...	—	—	—	+	+	—	+	—
17	M	64	167	66	27	0	B	179	183	157	146	155	—	—	—	+	+	+	+	—
18	F	84	...	56	15	0	B	...	...	...	...	...	+	—	—	—	+	+	+	+
21	F	67	158	68	14	12	B	211	143	124	136	155	+	—	—	—	+	+	+	+
22	M	65	...	78	19	20	A	...	...	...	167	122	+	+	+	+	+	+	+	+
24	M	40	194	86	7	96	O	...	...	...	...	...	—	—	—	—	+	+	+	—
26	M	59	175	79	13	40	A	238	211	179	172	155	—	—	—	—	+	+	+	+
27	M	51	174	88	16	40	A	254	231	211	165	158	—	—	—	—	+	—	—	—
29	F	32	165	67	24	72	O	386	416	435	...	...	+	+	+	+	+	—	—	—
30	F	73	...	...	3	20	A	326	284	271	225	...	—	—	—	—	+	—	+	—
34	F	57	168	72	16	0	B	...	...	...	...	...	—	—	—	+	+	—	+	—
41	M	71	171	65	15	20	A	252	207	198	205	177	+	+	+	—	+	+	+	—
42	M	63	179	88	26	56	A	...	...	...	...	...	—	—	—	—	+	+	+	—
43	M	67	181	94	7	20	B	176	164	129	132	113	—	—	—	+	+	+	+	+
45	F	30	159	55	24	48	O	...	...	...	...	...	—	—	—	+	+	—	+	—
47	M	43	181	80	22	72	A	491	508	484	492	486	+	+	+	—	+	+	—	—
49	F	16	170	60	5	88	O	...	...	...	...	...	—	—	—	—	+	—	+	—
50	M	25	172	62	4	40	O	...	...	...	...	...	—	—	+	—	+	—	—	—
51	M	21	171	64	1	0	A	132	110	96	92	75	—	—	—	—	+	—	+	—
52	F	59	159	55	1½	64	A	325	254	282	240	237	—	—	+	—	+	+	+	—
53	F	35	172	73	16	52	O	...	...	...	...	...	+	—	..	—	+	—	+	—
61	M	63	170	89	5	0	A	162	136	115	106	96	—	—	..	—	+	—	+	—
62	M	31	179	57	13	24	B	223	196	171	158	134	—	—	—	—	+	+	—	+
68	M	43	190	77	10	64	A	247	184	210	148	144	—	—	—	+	+	+	+	—
70	M	66	166	72	9	40	A	258	225	200	223	160	—	—	—	—	+	—	—	—
71	F	72	167	58	2½	20	B	315	237	230	200	211	+	—	+	—	+	—	—	—
72	M	57	172	75	½	0	A	211	179	158	125	125	—	—	..	—	+	—	—	—
74	F	60	152	52	2½	24	A	178	184	164	141	169	+	—	—	—	+	—	+	—
75	F	63	166	61	13	24	A	299	254	233	212	207	+	—	—	+	+	—	—	—
76	M	58	185	99	18	96	A	...	...	...	...	...	+	+	..	+	+	—	—	—
78	M	64	175	97	9	20	B	...	...	...	...	...	—	—	+	—	+	+	+	—
80	M	61	165	72	12	24	A	220	200	176	193	162	+	—	+	+	+	+	+	+
81	F	66	162	70	11	24	A	350	294	211	200	207	—	—	+	—	+	+	+	+
83	F	80	168	67	17	20	A	...	...	...	...	...	+	+	+	—	+	+	+	—
84	M	59	162	67	¼	0	B	162	125	108	103	125	+	—	—	—	+	—	+	—
86	M	32	179	67	1	48	B	275	230	226	191	169	—	—	—	—	+	—	+	—
87	M	33	172	68	3	48	A	251	225	172	197	184	—	—	—	—	+	—	—	—
88	F	51	172	77	12	12	A	259	205	218	171	155	+	—	—	+	+	—	+	—
89	F	28	161	63	16	72	O	...	...	...	...	...	—	—	+	—	+	+	+	—
92	F	57	158	53	1	88	A	352	315	298	306	287	+	—	—	+	+	—	—	—
93	F	22	158	58	17	88	O	...	...	...	...	...	—	—	—	—	+	—	—	—
94	F	28	162	61	13	64	O	378	...	...	...	...	—	—	—	—	+	—	—	—
99	F	64	164	57	10	24	A	219	184	153	151	115	—	—	..	—	+	+	+	+
100	F	31	155	58	21	64	O	...	...	...	...	...	—	+	+	—	+	—	—	—
102	F	44	172	84	13	72	A	...	...	...	...	...	—	—	+	—	+	+	+	—
108	M	49	176	74	17	80	O	...	...	...	...	...	—	—	+	—	+	+	+	+
109	M	66	179	77	8	32	A	244	209	153	146	143	+	—	+	—	+	+	+	+
112	F	50	155	58	10	0	B	275	221	216	204	138	+	—	+	—	+	—	—	+
114	F	44	177	62	¾	40	A	268	225	212	174	132	—	—	—	—	+	—	—	—
115	M	56	186	81	26	80	A	...	...	...	...	...	+	—	..	—	+	+	+	—
116	F	64	160	70	10	0	B	...	...	...	...	...	+	+	..	+	+	+	+	+
117	F	65	149	53	15	12	A	329	...	397	...	...	+	+	+	—	+	—	+	—
119	F	39	176	83	14½	72	O	...	...	...	...	...	—	—	+	—	+	—	+	—
122	M	45	177	..	9	12	A	223	186	183	176	153	+	+	..	—	+	—	+	—
129	F	62	160	75	4½	40	A	385	277	249	198	176	—	—	—	—	+	—	+	—
130	M	29	167	72	17	72	O	...	...	...	...	...	—	—	+	+	+	—	+	—
133	M	44	176	72	15	48	A	254	223	254	247	199	—	+	+	+	+	+	+	+
137	F	64	165	58	13	40	O	475	442	425	392	397	+	—	..	..	+	+	+	—
139	M	66	174	71	3	80	A	273	247	216	238	211	+	—	..	..	+	—	+	—
140	F	53	161	53	¼	72	A	329	317	169	208	220	—	—	+	+	+	—	—	—
146	M	60	174	92	21	48	A	225	235	198	204	167	—	—	+	+	+	+	+	+
147	M	47	180	69	19	80	O	380	390	390	270	414	—	—	+	+	+	+	+	+
149	F	29	174	58	8	64	O	...	...	...	...	...	—	+	+	—	+	—	+	—
158	M	23	180	69	8	88	O	...	...	...	...	...	—	—	+	—	+	+	—	—
159	M	40	180	71	14	84	O	...	...	...	...	...	+	—	+	—	+	—	—	—

* *O* indicates severely ketogenic diabetes; *A*, moderately ketogenic, and *B*, nonketogenic.

† A fasting day was contraindicated in cases in which rates are not given.

‡ The + sign indicates that the systolic blood pressure was over 160 mm. of mercury.

TABLE 2.—*Summary of Data on Diabetic Patients Without Neuritis*

Case No.	Sex	Age, Yr.	Height, Cm.	Weight, Kg.	Diabetes: Duration, Yr.	Diabetes: Insulin	Diabetes: Ketogenic Character*	Fasting Blood Sugar, Mg./100 Cc.†: 9 A. M.	12 A. M.	2 P. M.	4 P. M.	6 P. M.	Blood Pressure‡	Albuminuria	Retinopathy
4	M	56	174	73	22	40	A	235	186	202	198	181	+	—	—
5	M	64	179	81	5	8	A	202	160	162	190	99	—	—	—
7	M	57	167	53	11	88	O	...	...	...	...	...	—	—	—
11	F	34	171	70	1¼	40	A	181	155	144	138	83	—	—	—
14	F	16	168	51	6	80	O	204	171	160	151	102	—	—	—
16	F	76	166	64	25	100	O	...	...	...	...	...	+	—	+
19	M	70	162	66	23	16	B	222	188	155	165	151	—	—	—
20	F	48	168	72	½	16	B	265	164	146	118	101	+	—	—
23	M	47	181	67	13	72	O	...	...	...	...	...	—	—	—
28	F	39	175	81	12	48	O	...	...	...	...	...	—	—	—
31	M	56	178	54	1	64	A	165	96	99	85	108	—	—	..
33	F	54	166	52	6	96	O	277	201	147	199	181	—	—	+
35	M	39	179	87	1	0	B	131	104	113	101	96	—	—	—
36	F	59	160	62	1	0	B	216	184	165	155	122	+	—	—
37	F	62	169	61	4	20	A	287	270	256	197	197	+	+	+
38	F	24	165	70	16	80	O	...	...	...	...	...	—	—	—
39	F	13	162	44	1	40	A	235	184	104	96	84	—	—	—
40	F	24	162	58	2	48	O	228	171	200	190	174	—	—	—
44	M	29	188	50	7	72	A	219	198	158	163	153	—	—	—
46	M	26	175	70	1	20	A	221	162	160	134	113	—	—	—
48	M	41	175	69	1	20	A	256	244	214	196	146	—	—	—
54	F	43	168	69	1½	48	A	268	249	242	230	188	—	—	—
55	F	67	157	62	3½	24	B	240	205	165	153	125	—	—	—
56	F	60	162	58	6	20	A	298	259	237	237	219	+	—	—
57	M	13	162	47	¼	24	A	200	146	110	92	78	—	—	—
58	F	69	162	52	14	40	A	...	...	...	...	...	+	+	+
59	M	40	180	69	5	32	O	280	247	232	256	271	—	—	—
60	M	61	172	86	7	24	A	200	167	141	136	122	+	+	—
63	F	31	178	60	1	80	O	249	202	183	148	150	—	—	—
64	F	32	...	69	2	88	O	...	...	...	...	...	—	—	—
65	M	52	176	73	1	20	B	153	146	104	113	113	—	—	—
66	M	46	170	55	3½	16	A	99	108	103	85	89	+	—	—
69	M	37	177	77	8	64	O	...	...	...	...	...	—	—	+
73	F	34	169	69	12	96	O	...	...	...	...	...	—	—	—
79	M	59	174	89	4	0	B	200	171	143	129	113	+	—	—
82	F	19	158	59	15	96	O	...	...	...	...	...	—	—	+
85	F	47	167	58	2½	24	A	258	214	158	144	110	—	—	+
90	F	40	169	62	1	48	A	294	151	122	115	89	—	—	—
91	M	56	166	65	1½	64	A	297	346	309	327	312	—	—	—
94	M	36	177	56	5	48	A	156	111	97	84	70	—	+	—
95	F	63	166	71	4½	0	B	214	181	148	141	132	+	—	—
98	F	49	162	70	1	0	B	132	125	110	99	92	—	—	—
101	F	41	178	69	½	48	A	244	196	188	160	139	—	—	—
104	F	54	161	84	24	72	O	...	...	...	...	...	+	—	—
106	F	74	156	70	5	0	B	190	146	110	106	124	+	—	—
107	F	34	166	66	9	80	O	...	...	...	...	...	+	—	—
108	F	61	...	66	27	48	O	...	...	...	...	...	+	—	—
110	F	25	158	70	13	56	O	329	327	261	247	226	—	—	—
111	M	51	173	87	13	0	A	244	231	221	179	198	+	—	..
113	M	59	184	81	¾	24	A	221	198	160	144	133	—	—	—
118	F	30	155	60	5½	72	O	...	...	...	...	...	—	—	—
120	M	50	173	80	4½	96	A	219	172	172	178	138	—	+	—
121	F	57	167	108	½	0	B	255	120	103	124	86	+	—	—
123	M	12	...	..	9	32	O	146	146	80	104	96	—	—	—
124	M	55	177	68	17	64	O	...	...	...	...	...	—	—	+
125	M	46	174	90	¼	12	B	348	186	120	117	70	—	—	—
126	F	16	157	53	½	0	B	141	85	75	75	75	—	—	—
127	M	64	169	63	½	12	A	238	188	191	150	158	+	—	—
128	M	7	...	..	2	40	A	404	322	402	329	390	—	—	—
131	F	35	...	..	12	80	O	...	...	...	...	...	—	—	..
132	F	62	153	48	3	40	A	263	256	231	219	226	—	—	—
134	F	72	170	75	11	76	A	258	225	209	190	202	+	—	..
135	F	27	161	54	¼	40	A	230	188	183	171	155	—	—	—
136	F	60	159	70	3	12	A	193	173	129	134	127	+	—	—
138	M	42	184	67	10	28	A	271	212	202	197	179	—	—	+
141	M	25	182	72	½	40	A	218	198	200	134	146	—	—	..
142	F	23	167	59	8	96	O	...	...	...	...	...	—	—	+
143	F	56	171	72	5	0	A	282	245	200	172	178	+	—	—
144	F	38	163	66	¼	40	A	278	271	254	219	170	—	—	—
145	F	54	150	61	½	20	A	263	219	183	134	120	—	—	—
150	F	30	162	54	½	64	O	346	...	...	...	...	—	—	—
151	M	45	180	71	6	72	O	437	412	439	...	...	—	—	—
152	F	40	168	82	10	64	O	...	...	...	...	...	—	—	—
153	M	27	186	64	1	88	O	256	256	254	235	233	—	—	—
154	F	29	166	62	14	80	O	190	150	145	140	170	—	—	..
157	F	62	166	49	11	48	A	242	238	190	160	153	—	—	+

* *O* indicates severely ketogenic diabetes; *A*, moderately ketogenic, and *B*, nonketogenic.
† A fasting day was contraindicated in cases in which rates are not given.
‡ The + sign indicates that the systolic blood pressure was over 160 mm. of mercury.

reflexes. The patellar reflexes were absent, in one or both legs, in 37 patients (50.0 per cent of the neuritic patients) and appreciably attenuated in another 30 (40.5 per cent). The achilles tendon reflexes were absent in 48 patients (64.9 per cent) and appreciably attenuated in 19 (25.7 per cent) more. In the upper extremities the tendon reflexes were absent or appreciably attenuated in 29 patients (39.2 per cent). In all the instances the disturbance of tendon reflexes in the lower extremities was rated as the significant objective sign. Paresthesia was more evenly distributed, with only a slight prevalence in the lower extremities. Hyperesthesia and numbness in the region of the ulnar nerve, a burning sensation in the legs or a pricking one in the toes and plantar dysesthesia were common. Pain, indefinite or boring in character, and muscle tenderness prevailed in the lower extremities. The cutaneous sensibility was blunted in 31 patients (41.9 per cent), 9 of

TABLE 3.—*Age Distribution of Diabetic Patients With and Without Neuritis*

Age Groups, Years	Numbers of Patients	Percentages of Totals	Numbers of Neuritic Patients	Percentages of Neuritic Patients Within the Age Group
1-10	1	0.7	..	0.0
11-20	8	5.3	2	25.0
21-30	23	15.3	11	47.8
31-40	26	17.3	12	46.2
41-50	21	14.0	9	42.9
51-60	34	22.7	17	48.6
61-70	29	19.3	18	62.1
71-80	7	4.7	4	57.1
Over 80	1	0.7	1	100.0
Totals	150	100.0	74	..

these presenting areas of complete anesthesia. The vibratory sense over the tibia was absent in 30 patients (40.6 per cent). Definite disturbance of the joint sensation or the kinetic sense was not observed in the present series. Moderate ataxia was noted in 5 patients; this was cerebellar rather than spinal in character. A sluggish reaction of the pupils to light was found in 21 patients (28.4 per cent), this reaction being very pronounced in 3 of them. No true Argyll Robertson pupil was discovered. One patient had a mild paresis of the abducens nerve. Four patients were found to show muscular atrophy entailing the corresponding degree of paresis. In 2 of the patients the interosseous muscles of both hands were rather asymmetrically affected; the diabetic origin of this condition was doubtful. In another patient the extensor, and in still another the flexor, group of one leg was affected. Gangrene was observed in 5 patients, consistently associated with arteriosclerotic symptoms.

Among patients not included in the neuritic group, slight pupillary abnormality was noted in 5. About one third of the diabetic patients

without objective signs of neuritis complained of various paresthesias and pains.

Within the entire series of 150 diabetic patients a trophoneurotic complication, viz., Dupuytren's contracture of the palmar fascia, was found to be present in 5 patients (3.3 per cent). Two of these patients suffered from neuritis; the remaining patients did not present other nervous symptoms.

Behavior of the Blood Sugar.—The blood sugar values were estimated on a fasting day without insulin at 9 a. m., 12 noon and 2, 4 and 6 p. m. The findings convey a clear picture of the efficiency of endogenous blood sugar regulation. A comparison was made between the values recorded in patients with and without neuritis respectively. The means and standard errors were calculated from blood sugar estimations made in both groups. The data are given in table 4. The average blood sugar

TABLE 4.—*Variation of Average Blood Sugar Level from 9 a. m. to 6 p. m. During a Fasting Day in Diabetic Patients With and Without Neuritis (Statistical Evaluation of Individual Values Detailed in Tables 1 and 2)*

	Patients with Neuritis					Patients Without Neuritis				
Time of Estimation	9 A. M.	12 A. M.	2 P. M.	4 P. M.	6 P. M.	9 A. M.	12 A. M.	2 P. M.	4 P. M.	6 P. M.
Means of blood sugar level in mg. per 100 cc.	274	240	220	200	181	240	197	178	160	149
Standard error of mean	±12.2	±12.3	±12.2	±10.4	±10.9	±8.0	±7.7	±8.5	±7.1	±7.6
Standard error in percentage	±4.5	±5.1	±5.5	±5.2	±6.0	±3.3	±3.9	±4.8	±4.4	±5.1

level was considerably more elevated in the neuritic than in the non-neuritic group.

Significance of Ketone Bodies.—The diabetes was rated as types O, A and B according to Möllerström.[12] This classification was based on the degree of propensity toward ketone body excretion and coma. In carrying out the rating the aforementioned testing conditions were strictly maintained. The gravest type of diabetes is represented by type O in which ketone bodies are produced to such an extent that the endogenous regulation is insufficient to counteract acidosis and in which coma would inevitably ensue from a relaxation in insulin administration. In the present series 52 patients exhibited this severe type of diabetes, 24 (46.2 per cent) of whom had neuritis. The main characteristic of type A was the production and elimination of ketone bodies if insulin was not given but the endogenous regulation was perfectly capable of preventing coma. Of all the patients in the series, 72 were proved to be suffering from this moderately ketogenic form of diabetes, 37 (51.4 per cent) of whom had neuritis and 35 (48.6 per cent) of whom did not. In the remaining 26 patients diabetes was of type B. Dis-

tinctive of this type was, in the main, the disturbance of the alimentary blood sugar regulation. On a fasting day, or with an unrestricted diet, in either case without insulin, elimination of ketone bodies was never observed in patients of this type. Of the 26 patients with this mild type of diabetes, in 13 (50 per cent) neuritis developed and in the remaining 13 (50 per cent) neuritis did not develop. Hence, patients with and without neuritis were almost evenly distributed between the ketogenic and nonketogenic types of diabetes.

Duration of Diabetes and Age at Onset.—For a more accurate evaluation of the findings recorded in the preceding section it is necessary also to take into account the duration of diabetes. Unfortunately, precise data were not available as to the onset of the neuritis. Data pertaining to the duration of the diabetes had, therefore, to serve for comparison. In table 5 the duration of diabetes is given for the separate

TABLE 5.—*Average Duration of Diabetes at Time of Examination in Patients With and Without Neuritis, with Special Reference to Ketogenic Character of Disease*

Ketogenic Character	Patients with Neuritis			Patients Without Neuritis		
	Average Duration, Years	Standard Error		Average Duration, Years	Standard Error	
		Years	Per Cent		Years	Per Cent
Severe	14.6	±1.10	± 7.57	10.4	±1.29	±12.47
Moderate	10.0	±1.28	±12.77	4.3	±0.78	±18.08
Nonketogenic	9.8	±1.94	±19.69	3.5	±1.19	±33.64

groups of patients. The groups of patients with and without neuritis are subdivided according to the ketogenic trend of the diabetes (types O, A and B). The groups of patients with clinical evidence of neuritis had a history of diabetes of roughly ten to fifteen years on an average, and those without neuritis, of about four to ten years. This is in no way remarkable, but two details emerging from table 3 deserve closer consideration. The first is the fact that the smallest difference in the duration of diabetes between the groups with neuritis and without neuritis was found in the subgroup severe (type O). The figures are 14.6 and 10.4 years respectively, and the difference is 28.8 per cent. For patients with a diabetes nonketogenic in character, the corresponding figures are 9.8 and 3.5 years respectively, and the difference is 64.2 per cent. The second point of particular interest is that patients with the most ketogenic type of diabetes (type O) gave the longest and those with the most benign type (type B) the shortest history of diabetes. This observation might be explained by the different ages at onset in the separate types of diabetes (table 6). In the present series, the typical age at onset was for the most ketogenic form (type O) the third decade and for

the least ketogenic form (type B) the end of the fifth and the beginning of the sixth decade.

Thus a combined analysis of the data presented in tables 5 and 6 will show that in the present series the age of the patient (with arteriosclerosis and/or other conditions) seems to play a more conspicuous part in precipitating neuritis than does the acidosis.

Body Measurements.—The heights and weights of diabetic patients with and without neuritis were compared. Statistical evaluation showed that there was practically no difference between the two groups. The average height of the patients with neuritis was 169.3 (± 1.16) cm. and of those without neuritis 169.0 (± 1.01) cm. The corresponding figures for weight were 70.2 (± 1.39) and 66.9 (± 1.46) Kg. respectively.

TABLE 6.—*Average Age at Onset of Diabetes in Patients With and Without Neuritis, with Special Reference to Ketogenic Character of Disease*

Ketogenic Character	Patients with Neuritis			Patients Without Neuritis		
	Average Age, Years	Standard Error		Average Age, Years	Standard Error	
		Years	Per Cent		Years	Per Cent
Severe	20.2	±2.58	±12.79	26.8	±2.36	±8.79
Moderate	46.0	±2.27	± 4.94	42.1	±2.72	±6.45
Nonketogenic	48.8	±4.15	± 8.50	50.2	±3.15	±6.28

COMMENT

It is hardly possible to divide, with exact limits, diabetic patients into neurologically normal and pathologic groups. I was well aware that some overlapping was not to be avoided in considering objective signs of peripheral neuritis only; this seemed to be, however, the safest way to minimize this overlapping.

The neuropathic patients in this series comprise two groups according to the recent classification of diabetic neuropathy by Treusch,[13] viz., "ischemic neuropathy" and "diabetes polyneuritis." No such subdivision was made in my material. This was done not with the intention of denying the important role of circulatory disturbances but because common factors in the diabetic background were to be analyzed. It was supposed that a deficiency in circulation is mainly a precipitating factor, as it is generally known that neuritis often occurs in young diabetic patients without appreciable circulatory abnormality and, likewise, arteriosclerosis in older patients is very often not associated with neuritis. Nutritional deficiencies and poor management of treatment should

13. Treusch, J. W.: Diabetic Neuritis—a Suggested Classification, Ann. West. Med. & Surg. **1**:67, 1947.

naturally also be considered significant as being conducive to, or precipitating, the action of the really decisive factor in the diabetic background.

In the present investigation special attention was paid to the endogenous mechanisms of diabetes. The investigation was performed under conditions revealing the degree of metabolic alteration in interdependence with the internal compensation. The analysis served as a basis for assessing the closeness of the connection of these mechanisms with neuropathy.

The behavior of the blood sugar is of paramount interest regarding the problems of diabetes. When the individual values in tables 1 and 2 are considered, a certain overlapping between the two groups is apparent. This experience tallies well with the generally acknowledged fact that that there is no direct connection between blood sugar and neuritis. Yet the tendency toward higher rates in neuritic patients points to some correlation between the blood sugar and the neuritis. It should be strongly emphasized, however, that this correlation does not imply that a high blood sugar level leads in one way or the other to neuritic injury. On the contrary, according to Möllerström,[12] there is some evidence tending to suggest that an elevation of the blood sugar level in diabetes in certain respects is a defense mechanism. This supposition is *inter alia* based on the fact that in many cases reciprocity obtains between blood sugar level and glycosuria, on the one hand, and elimination of ketone bodies, on the other, as a rise in the blood sugar rate and a corresponding increase in the urinary excretion of sugar may be accompanied with a decreased excretion of ketone bodies and vice versa (first and second days in the chart). The difference in the average blood sugar level between diabetic patients with neuritis and those without neuritis is the expression of a factor acting from a deeper level in the disturbed metabolism. Therefore it seems dangerous to draw the conclusion for the management of diabetes that the elevated blood sugar level should be depressed in all cases and at any price to avert nervous complications. The individual structure of a given patient with diabetes should be very carefully considered.

Regarding ketone bodies, it emerged that the number of patients suffering from ketogenic diabetes was practically the same in the neuritic as in the non-neuritic group. Moreover, a comparison of the duration of ketogenic and nonketogenic diabetes in various patients suggests that the ketone bodies alone have no precipitating effect in the origination or maintenance of neuritis.

As the average weight and average height were practically identical in patients with and patients without neuritis, no further computation of ratios was made. A detailed study of my material, however, revealed the necessity for a further rating of diabetic patients according to build

of body. My material is too incomplete to allow a statement of any sort about this question; yet it seems that the incidence of neuritis is higher among young patients with an obese and dysplastic habitus. This observation needs further confirmation. It directed my attention toward the problem of the connection between diabetic lipemia and diabetic neuritis. An investigation into this matter is proceeding and will be the subject of a future communication.

SUMMARY AND CONCLUSIONS

A homogeneous series of 150 persons with diabetes was analyzed under uniform conditions in order to find out how closely factors in a diabetic background are connected with development and maintenance of neuritis. In 74 patients (49.3 per cent) objective symptoms of diabetic neuritis were noted, whereas no neuritic involvement was found in the remaining 76 patients. An attempt was made to establish a relation between the diabetic neuritis, on the one hand, and the blood sugar level, ketone body excretion and body habitus, on the other. It emerged that there was a certain relation between the sugar content of blood and the neuritis, in that the patients with neuritic involvement on an average had a higher blood sugar level than those without neuropathy. The import and the therapeutic aspects of this matter are discussed. Ketone bodies had no connection with these findings. An analysis of the build of body in our material yielded no definite results but supported the supposition that the incidence of diabetic neuritis is higher among young patients with an obese and dysplastic habitus.

ANOMALIES OF CORONARY ARTERIES

Report of Two Cases, with Comment on the Dynamics of Development of the Coronary Circulation

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CINCINNATI

ANOMALIES of development of the coronary arteries are not uncommon, and defects similar to the two described herein have been reported previously.[1] The presentation of these cases together was stimulated by the contrasting effects of the abnormal coronary arteries on the myocardium in the two cases.

REPORT OF CASES

CASE 1.—A white male infant, 5 months of age, was irritable and cried considerably during one morning; his temperature was 100.4 F. Early in the afternoon, he became stuporous, and a physician was called, but the baby was dead when the physician arrived.

The infant had been seen by the doctor four days before his death, and no abnormalities were noted during a complete examination at that time. After the death of the baby, the grandmother stated that he had been irritable and that his cry had been weak for two or three weeks prior to his death. The mother of this infant had never had rubella.

At autopsy the body was observed to be well developed and well nourished. The peritoneal cavity contained approximately 100 cc. of pale yellow thin fluid and throughout the body the areolar tissues were slightly edematous.

The pericardial sac filled the entire lower portion of the left pleural cavity. The heart weighed 80.5 Gm.[2] The left ventricle was greatly enlarged, and it bulged to the right and posteriorly, so that the right ventricle was rotated into a left and anterior position. The conus arteriosus was prominent, comprising the upper left surface of the front of the heart. The upper end of the anterior sulcus was located behind the obtuse border at the atrioventricular groove, whence this sulcus curved downward around the obtuse border, ending on the anterior surface at the apex. Approximately one tenth of the posterior surface of the heart consisted of the wall of the dilated left ventricle (fig. 1). The posterior sulcus was shifted to the right and anteriorly, so that it was on the anterior aspect of the heart. The posterior surface of the left ventricle was discolored in two areas; there was a

From the Kettering Laboratory, University of Cincinnati, and the Coroner's Office of Hamilton County, Ohio.

1. (*a*) Lyon, R. A.; Johansmann, R. J., and Dodd, K.: Anomalous Origin of Left Coronary Artery, Am. J. Dis. Child. **72**:675-690 (Dec.) 1946. (*b*) Krumbhaar, E. B., and Ehrich, W. E.: Varieties of Single Coronary Artery in Man, Occurring as Isolated Cardiac Anomalies, Am. J. M. Sc. **196**:407-413 (Sept.) 1938.

2. Mean weight of the heart at this age is approximately 30 Gm.

grayish yellow, slightly depressed area 2.5 by 1.6 cm., and this was surrounded by a reddish purple zone up to 0.3 cm. wide. There were a few small superficial hemorrhages in the purple zone. A similar region was located in the wall of the left ventricle immediately adjacent to the central portion of the anterior sulcus; the central yellow area was 1.1 by 0.8 cm. and the reddish purple zone around it was up to 0.8 cm. wide. Sections revealed the wall of the heart to be thin and fibrotic in the discolored areas. There was diffuse interstitial fibrosis of the myocardium of the left ventricle, and this fibrosis was especially prominent near the endocardium. The myocardium of the right ventricle was pinkish brown; the thickness of the myocardium was up to 0.4 cm. The interventricular septum averaged 0.9 cm. in thickness. The wall of the left ventricle varied in thickness up to 0.8 cm. in the areas adjacent to the septum.

The foramen ovale was present as a narrow elliptic orifice 0.1 cm. long. The endocardium of the right atrium and ventricle was thin and transparent. The right atrium was not dilated, and its myocardium appeared normal. The chamber

Fig. 1 (case 1).—Heart and lungs, posterior aspect. *A. S.* indicates anterior sulcus which was rotated into a posterior position by the enlarged left ventricle; *In.*, regions of infarction; *R. V.*, right ventricle, and *L. V.*, left ventricle.

of the right ventricle was small, owing to encroachment by the bulging interventricular septum which resulted from the dilatation of the left ventricle. The entire endocardium of the left atrium was underlain by a zone of fibrous tissue up to 0.1 cm. thick. The chamber of the left ventricle was extremely dilated and the trabeculae carneae were flattened. The endocardium was smooth and there were no thrombi. Beneath the endocardium was dense, opaque, grayish white, fibrous tissue which varied up to 0.05 cm. in thickness.

The ostium of the right coronary artery was in the aorta, in a normal position in the anterior sinus of Valsalva. This artery was widely patent, and at a point 0.3 cm. from the aorta it divided into three major branches of approximately equal size. One of these branches passed to the right in the coronary sulcus, sending branches into the myocardium of the right atrium and right ventricle; this vessel could not be followed beyond the posterior sulcus of the heart. A second major branch passed downward over the right ventricle, and near the central region of the right ventricle it extended deep into the tissues of the myocardium. The

third major branch passed to the left onto the conus arteriosus, and, after dividing several times, all its branches dipped into the myocardium of the conus arteriosus.

The left coronary artery arose from the right branch of the pulmonary artery immediately distal to the bifurcation of the latter (fig. 2). The ostium was widely patent and the trunk of the vessel circled behind the aorta to a point 0.3 cm. from its origin, where the vessel divided into several large branches. One of these branches passed to the anterior sulcus of the heart and extended down this sulcus as the anterior descending branch. Another large branch curved around the coronary sulcus as the left circumflex branch. A third large branch of the main trunk of the left coronary artery divided almost immediately into a number of small branches which fanned out over the surface of the left ventricle. All the branches were patent. The ductus arteriosus was closed and there were no abnormalities of the great veins.

There was much passive hyperemia of the other organs of the body, but no other changes were noted.

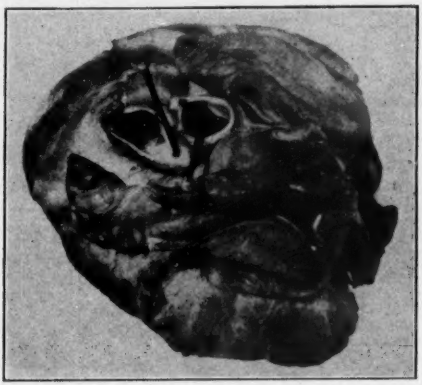

Fig. 2 (case 1).—Heart, superior aspect. The pin at the left is in the ostium of the anomalous left coronary artery, and the second pin is in the ostium of the right coronary artery.

Microscopic examination of the walls of the right atrium and ventricle of the heart revealed no myocardial fibrosis and the rami of the coronary arteries had normal walls. The epicardium and endocardium were normal.

A section through the wall of the left atrium revealed conspicuous thickening of the fibroelastic tissue beneath the intima. The myocardium was much thicker than usual and the muscle fibers were large with prominent, square-ended nuclei.

In that portion of the wall of the left ventricle immediately below the division of the left coronary artery, the myocardial fibers were small and were diminished in number. In addition, extensive areas of the myocardium were replaced by fibrous tissue which in some areas was calcified (fig. 3). There were a few lymphocytes and large mononuclear phagocytes scattered in the fibrous areas. In the myocardium and subjacent endocardium were a number of widely dilated vascular spaces, the walls of which were comprised of a single layer of endothelial cells. Some of these vascular spaces in the myocardium traversed areas of massive fibrosis, but almost invariably the tissues immediately adjacent to these spaces

contained muscle fibers, suggesting the possibility that the areas adjacent to the vascular sinuses were being nourished from blood within these sinuses. Study of serial sections revealed occasional small channels through which the sinuses communicated with the cavity of the left ventricle.

The branches of the left coronary artery had definitely thickened intimal coats and there were numerous clear vacuoles within the intima (fig. 4). The small branches of the coronary arteries within the myocardium had thickened medial coats and the smooth muscle fibers of their walls were in various stages of degeneration. The subepicardial connective tissues were dense and contained a few thin-walled vascular sinuses which anastomosed with those of the myocardium.

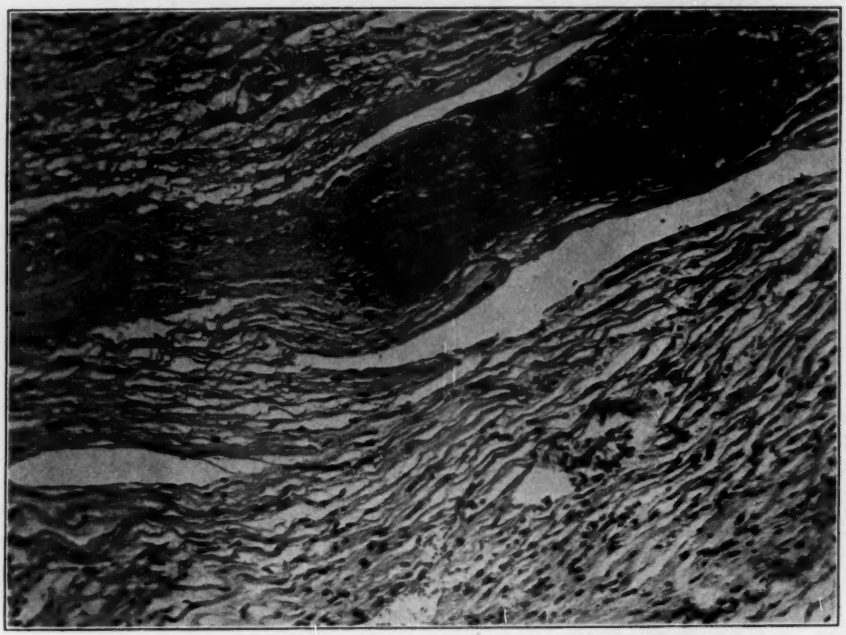

Fig. 3 (case 1).—Focus of calcification in myocardium of left ventricle. There are dense fibrosis in adjacent areas, diffuse interstitial fibrosis and degenerative changes of myocardial fibers; × 160.

The subendocardial connective tissues were thickened and dense, with extensive areas which contained relatively few fibrocytes, while in some focal areas the connective tissue was highly cellular. In some places the deepest fibers of the myocardium were undergoing pronounced degenerative changes, with various transition stages toward replacement fibrosis (fig. 5).

Sections through the two regions of marked thinning in the posterior wall of the left ventricle revealed complete fibrosis of the myocardium, with numerous foci of calcification. There were also extensive central areas of coagulation necrosis without associated acute inflammatory reaction. In the lateral portions of these

areas were regions of coagulation necrosis surrounded by myocardium in which decided degenerative changes were present. Foci of recent hemorrhage were seen in the myocardium near the periphery of the necrotic areas. One fairly large branch of the left coronary artery in the subepicardial connective tissue of one section showed extensive degenerative changes of the entire wall.

Sections through the interventricular septum revealed subendocardial fibrosis and deterioration of the myocardium immediately adjacent to the lumen of the left ventricle, while the remaining portion of the myocardium was unchanged.

Sections of pulmonary tissue revealed congestion of the capillaries and slight interstitial edema. There were occasional large mononuclear cells in the lumens

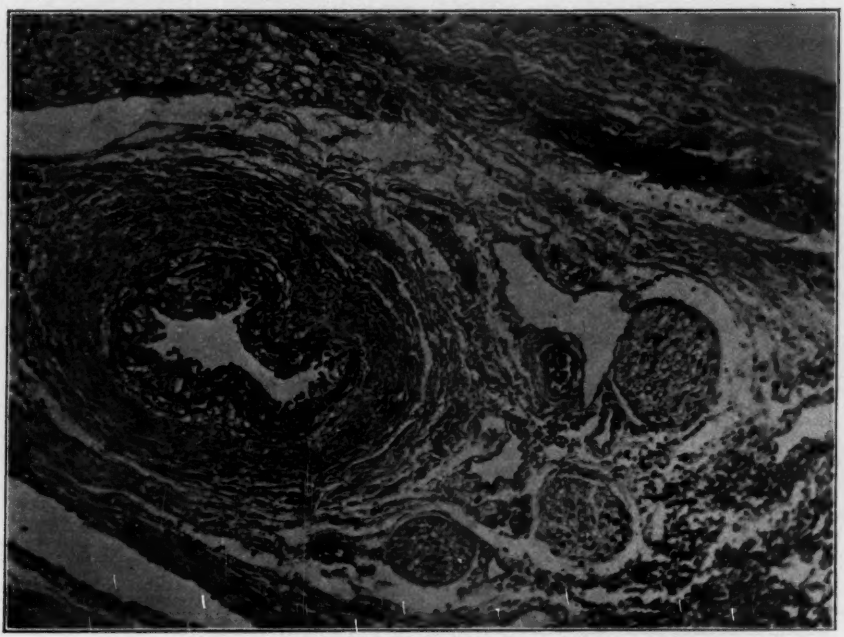

Fig. 4 (case 1).—Epicardial region of left ventricle, showing degeneration of media of small artery with thickening and vacuolation of the intima. Embryonic vascular sinusoids are visible in the adjacent connective tissues; × 160.

of the alveoli, and these cells contained granules of hemosiderin. The walls of the alveoli were slightly thickened and the cells lining the alveoli were large and had rounded surfaces.

Passive hyperemia of the liver was present to a notable degree and the cells in the central zones of the lobules were compressed by the dilated sinusoids. Many of the hepatic cells had small fat droplets in their cytoplasm.

The only abnormality of the other viscera was pronounced passive hyperemia.

The anatomic diagnosis was abnormality of left coronary artery, congenital (origin from right pulmonary artery); recent infarcts (two) of the myocardium of

the left ventricle; diffuse and focal fibrosis of the myocardium of the left ventricle; subendocardial fibrosis, left auricle and ventricle; hypertrophy and dilatation of heart; ascites, and passive hyperemia of viscera.

CASE 2.—A white woman, 49 years of age, was injured in an automobile accident. She died a few minutes after the accident. At autopsy, injuries of the chest were observed, with fractures of multiple ribs and of the sternum. There were lacerations of the left lung and hemothorax (left).

The heart weighed 320 Gm., and its only abnormality was an anomaly of the coronary circulation. The epicardium was thin and glistening. None of the chambers was dilated, and the walls of the chambers were of average thickness.

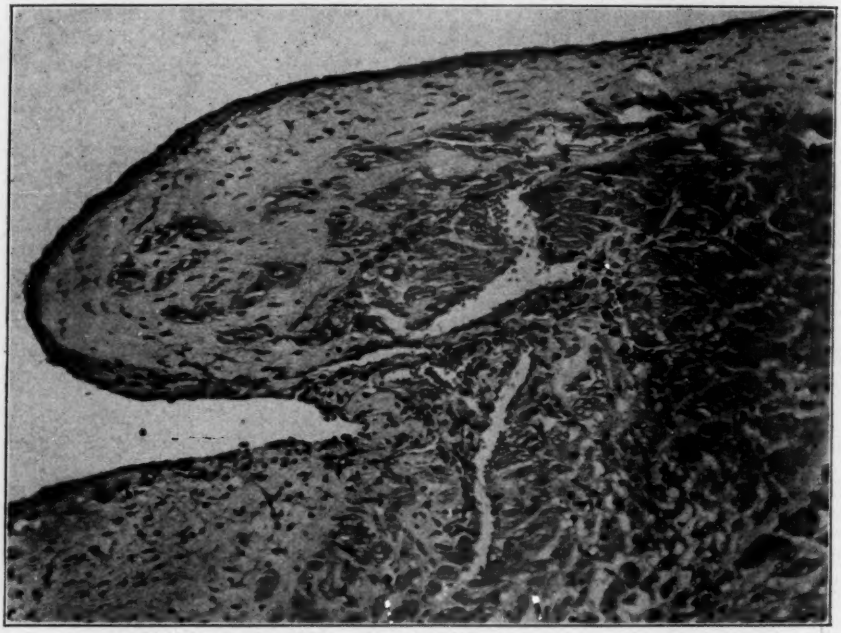

Fig. 5 (case 1).—Region of endocardium of left ventricle, showing thickened, dense subendocardial connective tissues in which are incorporated degenerating myocardial fibers; × 160.

There was no evidence of myocardial fibrosis. No left coronary artery was present. The right coronary artery arose in a normal fashion from the right anterior sinus of Valsalva and followed the usual course around the coronary sulcus. A fairly large branch from the right coronary artery arose 2 mm. from the point of origin of the latter and passed between the aorta and the pulmonary artery to the region of the anterior longitudinal sulcus, down which it could be dissected to within 4 mm. of the apex of the heart. In the sulcus, the vessel gave origin to a number of septal branches which dipped directly backward into the myocardium; there was no branch in the coronary sulcus which might have resembled the

circumflex branch of a normal left coronary artery. Several other branches from the right coronary artery extended down onto the anterior and posterior surfaces of the right ventricle. At the upper end of the posterior sulcus of the heart the right coronary artery bifurcated; one branch passed down the posterior sulcus as the posterior descending branch, while the other continued to the left to end in a number of terminal branches which fanned out over the posterior surface and obtuse border of the left ventricle. Several of the latter extended far around onto the lateral and anterior surfaces of the left ventricle. The right coronary artery and its branches were without sclerosis, and the vessels were widely patent. There was slight atherosclerosis of the intima of the aorta, without evidence of calcification or ulceration.

The anatomic diagnosis was injuries of the chest, with lacerations of left lung, hemothorax (left) and fractures of sternum and of multiple ribs; congenital absence of left coronary artery, and hyperplasia (supplementary) of right coronary artery.

COMMENT

The consideration of these 2 cases together illustrates an important principle relating to the development of supplementary circulation.[3] In the infant whose left coronary artery arose from the right pulmonary artery, the supply of oxygen to the myocardium of the left ventricle was insufficient to maintain the integrity of the tissues. In spite of the fact that the anoxia was of such a degree as to result in focal necrosis and fibrosis of the myocardium, there was no apparent tendency toward extension of branches from the right coronary artery into the wall of the left ventricle to compensate for this deficiency of oxygen.

On the other hand, in the second case the complete absence of the left coronary artery was accompanied with the development of supplementary branches from the right coronary artery to the left side of the heart, and there was no apparent functional or anatomic abnormality of the myocardium.

The stimulus that leads to the origin and development of new blood vessels is entirely unknown, and virtually no relevant experimental observations are available. There has been speculation that the growth of vessels into an area is prompted by the development, within the area, of chemical substances capable of stimulating their ingrowth. In considering the factors responsible for the development of collateral circulation to the myocardium during the gradual development of stenosis of coronary arteries, Wiggers[4] suggested that "the slow establishment

3. The term "supplementary circulation" is here preferred to "collateral circulation." The latter implies that compensation for suboptimal blood flow is effected by increased flow through preexisting vessels. "Supplementary circulation" is a more generic term, since it refers to any adjustment of the circulation which serves to prevent a local deficiency in oxygenated blood.

4. Wiggers, C. J.: Inadequacy of Normal Collateral Coronary Circulation and Dynamic Factors Concerned in Its Development During Slow Coronary Occlusion, Am. Heart J. **11**:641-647 (June) 1936.

of differential pressure gradients" during the development of stenosis or occlusion may lead to distention of "normally useless vessels to a degree that they soon become pervious to blood."

In dogs it has been observed that immediately after the ligation of a major coronary artery, the pressure in the distal segment falls to a low level.[5] It was also demonstrated that the blood pressure in the distal segments rose significantly during periods of forty-six to three hundred and sixty days after occlusion. In addition, the rate of flow from the peripheral segment was determined and the minute volume was much greater from arteries that had been ligated some weeks or months prior to the conclusion of the experiment than from arteries that had not been previously occluded. Gregg and his associates also observed that the blood which flowed from the distal ends of ligated coronary arteries had the characteristics of arterial blood, and that a large proportion of this blood was derived from anastomoses with branches of other coronary arteries.

The two contrasting cases reported here are believed to indicate the importance of pressure gradients in determining the development of arterial channels. In the infant, the myocardium of the left side of the heart was receiving only blood of relatively low oxygen tension through its anomalous left coronary artery. It is considered probable that the presence of blood under appreciable pressure in vessels within the myocardium of the left side of the heart was sufficient to prevent any tendency for an ingrowth of branches from the right coronary artery. In this connection, it is notable that in a young infant the pressures within the pulmonary artery are probably nearly identical with those in the aorta at any given phase of the cardiac cycle,[6] so that the pressures within the two coronary arteries are probably comparable during the short life spans of nearly all persons who have this anomaly.

An entirely different situation was present when there was congenital absence of the left coronary artery. This anomaly was associated with the development of branches from the right coronary artery which adequately supplied the left side of the heart with oxygenated blood. It seems reasonable to presume that the growth of such branches was promoted by the aplasia of a left coronary artery in which there would have been blood under pressure. In all other reported instances of congenital absence of one coronary artery, the development of supple-

5. Gregg, D. E.; Thornton, J. J., and Mautz, F. R.: Magnitude, Adequacy and Source of Collateral Blood Flow and Pressure in Chronically Occluded Coronary Arteries, Am. J. Physiol. **127**:161-175 (Aug.) 1939.

6. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947. Hamilton, W. F.; Woodbury, R. A., and Woods, E. B.: The Relation Between Systemic and Pulmonary Blood Pressures in the Fetus, Am. J. Physiol. **119**:206, 1937.

mentary arterial channels from the artery which was present prevented the development of myocardial degeneration or fibrosis.

The contrast of the origin and distribution of the coronary arteries in these 2 cases, and of the effects on the myocardium in each instance, lends support to the concept that one of the most important factors in the development of supplementary arterial channels may be the pressure gradient. The oxygen tension in the tissues seems to play no part in such development.

The instance of the left coronary artery arising from the right pulmonary artery reported here is unique in the medical literature, although 20 previous cases have been presented in which the ostium of the left coronary artery was in the main trunk of the pulmonary artery. Sixteen of these 20 persons died in infancy with evidences of anoxia of the left ventricle. Of the 4 who survived into adult life, 2 [7] had histories of angina pectoris; 1 [7a] died at the age of 38 years and his heart was observed to be enlarged, with foci of fibrosis in the myocardium. Both coronary arteries were enlarged and anastomotic channels connected small branches of the left with branches of the right. The second patient [7b] with angina pectoris died at 57 years; he had a large heart and there were numerous arteriosclerotic plaques in the intima of the right coronary artery. The left coronary artery was not sclerotic, but numerous nodular bodies were present in the wall of the vessel; in the author's opinion they represented myoneuroarterial glomera and were accepted as evidence of the presence of arteriovenous anastomoses. Such anastomoses were not demonstrated by anatomic or injection methods. One man [8] died suddenly while doing hard manual labor. The left coronary artery arose from the pulmonary artery, and the right from the aorta. The right artery was decidedly enlarged and there were many anastomoses between branches of the two arteries. In only one case [9] has the anomalous origin of the left coronary artery from the pulmonary artery been noted without associated myocardial damage.

There are few reported instances of congenital absence of a coronary artery. The literature on this subject has been reviewed by Krumbhaar and Ehrich,[1b] who tabulated 6 previously reported cases of absence of the right coronary artery and 6 of absence of the left. They

7. (*a*) Kockel, H.: Eigenartige Kranzschlagadermissbildungen, Beitr. z. path. Anat. u. z. allg. Path. **94**:220-226, 1934. (*b*) Dietrich, W.: Ursprung der vorderen Kranzarterie aus der Lungenschlagader mit ungewöhnlichen Veränderungen des Herzmuskels und der Gefässwände, Virchows Arch. f. path. Anat. **303**: 436-456, 1939.

8. Rübberdt, H.: Abnormer Abgang der linken Kranzarterie aus der Lungenschlagader, Beitr. z. path. Anat. u. z. allg. Path. **98**:571-578, 1937.

9. Abbott, M. E.: Congenital Cardiac Disease, in Osler, W.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, pp. 612-812.

also reported one case of each type of their own. No instance in which an anomaly of this type was responsible for myocardial damage was noted. In a case of aplasia of the left coronary artery which was reported by Smith and Graber[10] death resulted from acute thrombosis in a branch of the hyperplastic right coronary artery, and it is possible that this thrombosis might not have been fatal in the absence of such an anomaly.

It is believed to be significant, in considering supplementary blood supply to the myocardium, that in the 20 previously reported cases in which the left coronary artery was derived from the pulmonary artery there has been (with one exception) evidence of anoxia of the myocardium. Conversely, the congenital absence of one coronary artery has always been associated with adequate supplementary development of the artery which is present.[11]

The lesions in the heart in which the left coronary artery arose from the right pulmonary artery were similar to those observed in most cases in which the left coronary artery arose from the main trunk of the pulmonary artery. In nearly all cases of this type the heart has been enlarged, and it is interesting to note that the heart in one such case[12] was described as an example of "idiopathic hypertrophy." Most persons who have this anomaly die within their first year of life, and the death is not infrequently associated with serious myocardial fibrosis. Subendocardial fibrosis in the left auricle and ventricle has been observed in a number of hearts in which the left coronary artery arose from the pulmonary artery. Such fibrosis is believed to be related to the relative anoxia of the tissues as a result of the abnormal left coronary artery.

Sinusoids within the myocardium[13] and epicardium[14] have been described previously in hearts which have the left coronary artery arising from the pulmonary artery. In the opinion of Soloff,[13b] these represent persistent embryonic vascular channels which normally are reduced to form the capillary network as the myocardium develops.

10. Smith, F. M., and Graber, V. C.: Coronary Thrombosis with Congenital Absence of Left Coronary Artery, Arch. Int. Med. **38**:222-225 (Aug.) 1926.

11. In the case described by Sanes (Am. Heart J. **14**:219-229 [Aug.] 1937) there was myocarditis of unknown origin. The patient died of acute glomerulonephritis, and there were associated generalized edema, hepatitis, myositis (diaphragm) and splenitis. Sanes stated: "On an infectious-toxic basis, the cardiac lesion could fit in with changes in the liver, muscle and spleen."

12. Krumbhaar, E. B.: Anomalous Coronary from Pulmonary Artery, Internat. A. M. Museums Bull. **10**:108-111 (April) 1924.

13. (*a*) Lyon and others.[13a] (*b*) Soloff, L. A.: Anomalous Coronary Arteries Arising From Pulmonary Artery: Report of Case in Which Left Coronary Artery Arose from Pulmonary Artery, Am. Heart J. **24**:118-127 (July) 1942.

14. Proescher, F., and Baumann, F. W.: Abnormal Origin of Left Coronary Artery with Extensive Cardiac Changes in Female Child 13 Months Old, J. Pediat. **25**:344-350 (Oct.) 1944.

CONCLUSIONS

1. Two anomalies of the coronary arteries are reported, origin of the left coronary artery from the right pulmonary artery in one case and congenital absence of the left coronary artery in the other.

2. Origin of the left coronary artery from the pulmonary artery usually results in severe functional and anatomic abnormalities of the heart, while congenital absence of the left coronary artery is accompanied with the adequate development of supplementary branches from the remaining artery.

3. It is suggested that the development of supplementary circulation in the myocardium is not stimulated by local anoxia, but that pressure gradients may play a significant role in this phenomenon.

Eden Avenue (19).

BLOOD LIPID FRACTIONS AND DIABETIC NEURITIS

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THE HYPERLIPEMIA associated with diabetes mellitus is of particular interest because the level of the blood lipid constituents is, to a certain degree, an index of the fat metabolism and shows a relation to some clinical manifestations. In the present paper the relation between the diabetic neuritis and the blood lipid fractions, total fat, cholesterol and lipid phosphorus will be discussed.

Jordan, Randall and Bloor,[1] Jordan and Randall [2] and Randall [3] made determinations of phospholipids, cholesterol and cerebrosides in the femoral, sciatic and posterior tibial nerves of diabetic patients. They state that the lipid constituents in these nerves were considerably reduced as compared with the normal. The results obtained by the authors mentioned, and also the opinion advanced by one of us in a previous paper,[4] viz., that diabetic neuritis occurs especially in young, obese patients with a dysplastic habitus, led us to the investigation the results of which will be presented.

MATERIAL AND METHODS

The 46 diabetic patients serving as subjects for this investigation entered the research clinic only for a control examination, that is to say, their diabetes was well managed and regulated also prior to hospitalization. Each patient underwent a routine medical and neurologic examination and a clinical analysis of the

From the Department of Metabolic Research, Wenner-Grens Institut, Stockholms Högskola.

1. Jordan, W. R.; Randall, L. O., and Bloor, W. R.: Neuropathy in Diabetes Mellitus: Lipid Constituents of Nerves Correlated with Clinical Data, Arch. Int. Med. **55**:26-41 (Jan.) 1935.

2. Jordan, W. R., and Randall, L. O.: Neuropathy in Diabetes: Lipid Constituents of Nerves Correlated with Clinical Data, Arch. Int. Med. **57**:414-421 (Feb.) 1936.

3. Randall, L. O.: Changes in Lipid Composition of Nerves from Arteriosclerotic and Diabetic Subjects, J. Biol. Chem. **125**:723-728, 1938.

4. Bonkalo, A.: Relation Between Neuritis and the Clinical Background in Diabetes Mellitus, Arch. Int. Med., this issue, p. 944.

endogenous structure of the diabetes.[5] The diabetic patients were examined in turn as they came into the clinic during a period from August 1949 to November, and no special selection of patients was made. An exception was made if conditions were found which were known to elevate the lipemia or cause neurologic alterations definitely not connected with the diabetes; such cases were discarded. The diagnosis of peripheral diabetic neuritis was based on objective symptoms

TABLE 1.—*Plasma Lipids of Diabetic Patients Without Peripheral Neuritis in the Postabsorptive State*

Patient	Sex	Age	Type of Diabetes	Insulin Demand per Day, International Units	Total Fat, Mg./100 Ml.	Cholesterol, Mg./100 Ml.	Lipid Phosphorus, Mg./100 Ml.
H. J.	M	19	O*	64	730	326	8.40
I. B.	M	39	A*	64	975	356	6.10
A. E.	F	54	A	20	655	153	6.85
L. I.	F	41	B†	0	765	150	6.30
S. A.	F	38	A	40	850	250	7.10
B. T.	F	19	A	64	890	280	7.30
B. W.	M	24	O	72	845	290	7.35
B. A.	F	24	O	80	906	230	7.60
G. S.	M	42	A	28	707	268	7.75
M. S.	F	30	O	64	705	180	8.05
M. B.	F	24	O	48	820	296	8.05
B. A.	F	23	O	96	805	285	8.15
M. O.	F	31	O	80	810	250	8.51
I. B.	M	25	A	40	1,100	298	8.60
S. H.	F	64	O	64	795	190	8.90
H. M.	F	48	B	16	877	264	9.20
C. D.	M	38	A	64	970	340	9.40
S. A.	M	27	O	88	875	355	9.50
A. P.	F	37	A	88	1,005	340	9.65
S. L.	M	47	O	72	1,230	250	11.43
E. W.	F	62	A	48	900	295	11.75
V. L.	F	47	O	80	1,180	383	12.05
M. N.	M	45	O	72	1,420	380	14.00
Mean	..	37	..	59	908	279	8.56
Standard error of mean ‡					58	14	0.47

* Ketogenic diabetes; classification according to Möllerström (Möllerström, J.: Das Diabetesproblem, Acta med. Scandinav., 1943, supp. 147, pp. 1-476).

† Nonketogenic diabetes.

‡ $e\,(M) = \pm \frac{\sigma}{\sqrt{n}}$; $\sigma = \sqrt{\frac{\Sigma\,(M - x)^2}{n - 1}}$

only, pains of various types being disregarded. Each neuritic patient in our material had extinct or definitely attenuated patellar or achilles reflexes, and 7 of them, moreover, had disturbances of the cutaneous sensibility of the legs. A detailed description of the neurologic symptoms did not seem to be of further interest here, as the majority of subjects within our series also had figured in a previous paper dealing more closely with diabetic neuritis from the neurologic point of view.[4]

5. Möllerström, J.: Theoretical Considerations and Practical Results in the Management of Diabetes, Acta med. Scandinav., 1947, supp. 196, pp. 12-23.

The determination of blood lipid fractions was usually made in the last days of hospitalization when the diabetic patient had attained a metabolic balance with a sufficient dose of insulin and was on a diet corresponding to the common Swedish diet without restrictions as to the amount and composition. After a fasting period of ten to twelve hours, 20 ml. of blood was collected; and the content of total lipids (total fat), lipid phosphorus and total cholesterol in the plasma was estimated in the same way and under the same conditions as described by one of us in a previous communication on diabetic lipemia.[6] (Each figure is the mean of two parallel estimations.)

TABLE 2.—*Plasma Lipids of Diabetic Patients with Peripheral Neuritis in the Postabsorptive State*

Patient	Sex	Age	Type of Diabetes	Insulin Demand per Day, International Units	Total Fat, Mg./100 Ml.	Cholesterol, Mg./100 Ml.	Lipid Phosphorus, Mg./100 Ml.	Nervous Alterations: Tendon Reflexes	Nervous Alterations: Sensibility	Nervous Alterations: Trophic	
S. S.	M	23	A	80	820	290	6.40	+	—	—	..
C. N.	M	66	A	80	1,024	344	8.45	+	—	—	..
E. L.	M	57	A	0	925	300	8.79	+	—	—	..
R. M.	M	60	A	48	1,012	287	8.80	+	+	+	..
E. K.	M	40	O	84	900	275	8.85	+	—	—	..
K. N.	M	32	O	80	835	305	9.00	+	—	—	..
C. S.	M	42	A	64	840	253	9.14	+	+	+	..
B. P.	F	15	O	100	850	285	9.15	+	—	—	..
R. S.	M	43	O	72	1,015	340	9.65	+	—	—	..
M. K.	F	22	O	88	1,150	233	9.90	+	—	—	D *
K. A.	M	51	A	40	1,265	305	10.10	+	—	—	..
T. T.	F	64	O	40	1,300	265	10.15	+	+	—	..
E. M.	F	29	O	64	1,180	220	10.30	+	—	—	..
E. H.	M	27	O	88	1,205	390	10.75	+	—	—	..
A. W.	F	28	O	72	1,001	250	11.00	+	—	—	D
E. L.	F	44	A	32	895	340	11.20	+	—	—	D
F. C.	F	53	A	72	1,200	295	12.30	+	—	—	..
E. N.	M	23	O	88	1,335	437	12.80	+	+	—	..
V. C.	F	51	A	12	1,006	275	14.80	+	—	—	..
E. S.	F	50	B	0	1,107	360	15.15	+	—	—	..
B. B.	F	28	O	64	1,080	265	15.80	+	+	—	D
O. L.	M	66	A	32	782	225	15.85	+	+	+	..
L. S.	F	25	O	48	1,940	495	16.70	+	+	+	D
Mean	..	41	..	59	1,083	312	11.09	23	7	4	5
Standard error of mean					52	15	0.60	..	..	..	..

* Dysplastic habitus.

OBSERVATIONS

The diabetic patients examined by us were divided into two groups. To the first group were referred patients without any nervous complications, the data being recorded in table 1. This table relates to 23 diabetic patients, 14 women and 9 men, ranging in age from 19 to 64, on an average 37 years, and suffering from various types of diabetes. The

6. Širek, O. V.: On the Relationship Between Blood Lipids and the Excretion of Choline in Diabetic Patients, Arch. Int. Med. **85**:272-279 (Feb.) 1950.

mean of the total fat is 908 ± 38 mg., of cholesterol 279 ± 14 mg., and the mean of the lipid phosphorus 8.56 ± 0.47 mg. per hundred milliliters of plasma.

Table 2 deals with diabetic patients suffering from neuritis. The second group of patients also comprises 23 subjects, 11 women and 12 men, ranging in age from 15 to 66, on an average 41 years, and with various types of diabetes. In this group the mean rate for total fat is 1,083 ± 52 mg., for cholesterol 312 ± 15 mg. and for lipid phosphorus 11.09 ± 0.60 mg. per hundred milliliters of plasma. Table 2 shows further that there are subjects with a dysplastic habitus. All 5 obese diabetic patients were women, aged 22, 25, 28, 28 and 44 years, showing a pathologic adiposity of the Cushing type.[7] This subgroup represents 22 per cent of the 23 neuritic patients and 11 per cent of the entire series.

If table 1 and table 2 are compared, a certain tendency toward hyperlipemia will be apparent in diabetic patients with nervous alterations, while in those without nervous disturbances the figures show the tendency to keep within normal limits. These opposed tendencies in both groups are just appreciable regarding total fat, while in the case of lipid phosphorus they are striking. An exception are the rates of cholesterol which do not show any correlation to diabetic neuritis. These observations can also be established statistically. The difference between the means of both groups[8] is for total fat 175 ± 64 mg., for cholesterol 33 ± 21 and for lipid phosphorus 2.53 ± 0.36 mg. per hundred milliliters of plasma. The statistical valuation indicates that a significant difference obtains as to lipid phosphorus only, while the rates of total fat and mainly of cholesterol show a considerable overlapping.

COMMENT

It is difficult to divide, within definite limits, diabetic patients into neurologically normal and pathologic groups. The way to minimize this difficulty is to disregard subjective symptoms and to consider objective findings only, such as extinct or appreciable attenuated tendon reflexes, disturbances of the sensibility within anatomically well defined areas and trophic changes arising on a neurologic basis.

If we survey once more the results of our investigation, it seems to be established beyond doubt that there is a correlation between elevated plasma lipid phosphorus and diabetic neuritis. In this connection it is of interest that the cholesterol figures did not show any correlation with the diabetic neuritis, although in clinical practice the cholesterol is generally regarded as an accurate index of the lipemia, and the other lipid

7. Jores, A.: Klinische Endokrinologie: Ein Lehrbuch für Aerzte und Studierende, ed. 3, Berlin, Julius Springer, 1949, pp. 81-93.

8. Difference $= M_1 - M_2 \pm \sqrt{e\,(M_1)^2 + e\,(M_2)^2}$.

fractions are often neglected. It seems that the significance of the cholesterol in this respect must be considered with circumspection, and closer attention should be paid to the lipid phosphorus.

Arteriosclerosis is often mentioned in a causal connection with the peripheral neuritis in diabetes,[9] but all the authors experience difficulties in explaining the occurrence of neuritis even in young patients without any signs of arteriosclerosis. Also in our material there are 10 diabetic patients, who were younger than 40 years (average, 25 years) and showed objective symptoms of neuritis, while 8 patients were older than 40 years (on an average, 51 years) and were without any neuritic symptoms. Arteriosclerosis plays, undoubtedly, an important rôle in the onset and maintenance of diabetic neuritis, but there is some evidence that this is not due to arteriosclerosis only. A further support for the conception that other factors also take part in the maintenance of diabetic neuritis is the 5 diabetic patients with a pathologic obesity of the Cushing type.

In a previous paper concerning diabetic lipemia it was shown by one of us [6] that a higher amount of lipid phosphorus in the blood plasma was always followed by an increased excretion of choline, and, likewise, that patients with a normal level of lipid phosphorus showed a daily choline excretion within physiologic limits. On this basis it appears probable that also in this material the group of diabetic patients with neuritis will have an increased urinary choline output, while the group of patients without neuritis will show a normal choline excretion (on an average not over 5 mg. per day).

Apparently we are obliged to suppose that diabetic neuritis and the increased level of plasma phospholipids are manifestations in the syndrome complex of an abnormal fat metabolism and that the primary reason for the disturbance lies very deep and is connected in some way with the body's constitution. In this respect, perhaps, attention should be directed more toward the metabolic centers and the pituitary body.

SUMMARY AND CONCLUSIONS

In the present paper the relation between the maintenance of the peripheral neuritis and the blood lipid fractions as total fat, cholesterol and lipid phosphorus in 46 diabetic subjects is discussed. A tendency toward hyperlipemia has been apparent in diabetic patients with nervous alterations, while in those without them the rates have shown the tendency to keep within physiologic limits. This opposed tendency in both groups of patients was just appreciable regarding total fat, while

9. Kauvar, A. J.: The Relation of Arteriosclerosis to Diabetic Neuritis of the Lower Extremities, J. Clin. Endocrinol. 1:955-959, 1941. Jordan, Randall and Bloor.[1] Jordan and Randall.[2] Randall.[3]

in the case of lipid phosphorus the tendency was striking, and a statistically significant difference was also obtained. An exception were the cholesterol figures, which did not show any correlation to diabetic neuritis. Five patients with neuritis (11 per cent) had a dysplastic habitus with obesity of the Cushing type.

The significance of the relation between diabetic neuritis and the increased amount of phospholipids in the blood plasma and also the influence of arteriosclerosis are further discussed. The opinion is expressed that diabetic neuritis not only is due to arteriosclerosis but also is due to disturbances in the fat metabolism; in this regard attention should be directed more toward the metabolic centers and the pituitary body.

Mrs. Eva Lövgren gave technical assistance in this study.

INTRAVENOUS ADMINISTRATION OF TETRACAINE (PONTOCAINE®) HYDROCHLORIDE

Preliminary Report

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MEMPHIS, TENN.

DURING the last eight years numerous reports have been published on the intravenous use of procaine (novocain®) hydrochloride. In the United States interest has centered mainly on administration in the slow intravenous drip of 0.1 and 0.2 per cent solutions, taking from twenty minutes to an hour and a half. Results have been excellent in the treatment of many traumatic conditions, inflammatory states and pain syndromes. Unfortunately, however, the giving of an infusion of 500 cc. of solution by slow intravenous drip is not practical in a physician's office. It seemed advisable to search for a more potent solution that could be given quickly in small doses. Workers in Europe have reported on the use of 1 per cent solution of procaine hydrochloride intravenously, with good results. It has been given in treatment of asthma,[1] angina pectoris [1b] and numerous other conditions, usually in doses of 3 to 10 cc. The dose was not sufficient to control many painful conditions, however.

Accordingly, tetracaine (pontocaine®) hydrochloride,[2] a higher homologue of procaine hydrochloride, was selected for clinical trial. It is dibutyl-dimethyl-aminoethanol paraaminobenzoic acid hydrochloride and is about ten times as potent and ten times as toxic as procaine, on the basis of animal experiments.[3] Tetracaine is used as a topical anesthetic and has proved efficacious in ophthalmic and otorhinolaryngologic work; it has also been used extensively for induction of caudal and spinal anesthesia. Moore,[4] an anesthesiologist in Seattle, has

From the Department of Psychiatry and Neurology, College of Medicine, University of Tennessee.

1. (*a*) Ameuille, P.: Intravenous Administration of Novocain, Progrès méd. **73**:407 (Dec. 10) 1945. (*b*) Barfod, B.: Bronchial Asthma Treated with Intravenous Injections of Procaine Hydrochloride, Nord. med. (Hospitalstid.) **27**:1702 (Aug. 31) 1945.

2. This drug was furnished through the courtesy of Winthrop-Stearns, Inc., New York. Kiess, T.: Experience with a New Preparation—Pontocaine, Zentralbl. f. Chir. **57**:3090 (Dec. 13) 1930.

3. Tyler, E. A.: Preliminary Report on Pontocaine as a Regional Anesthetic, Hahneman. Monthly **68**:174 (March) 1933.

4. Moore, D. C.: Pontocaine Hydrochloride for Brachial Block Anesthesia: 150 Cases, Anesthesiology **9**:281-284 (May) 1948.

reported the production of one hundred and fifty brachial plexus blocks with 0.15 per cent solution of tetracaine, using 80 to 125 mg. without evidence of toxicity but with satisfactory anesthesia for five to six and one-half hours. I employed 0.15 per cent tetracaine solution, using from 7.5 to 100 mg. of the drug, more than one hundred times in infiltrations and in induction of nerve blocks, without any untoward reaction. This suggested that tetracaine might be given intravenously. Small amounts in great dilution were tried first, with gradually increasing doses, until one patient received 250 mg. in 500 cc. of isotonic sodium chloride solution. This apparently massive dose had no undesirable effect. Since an office procedure was sought for, the dose settled on was 10 cc. of 0.25 per cent tetracaine solution, given slowly over a period of three to five minutes. This has proved effective. In this preliminary work, a series of 104 patients received a total of 204 intravenous infusions of tetracaine for pain, itching, asthma and miscellaneous conditions. One patient fainted and 1 patient had slight nausea and vomiting. Some have complained of transient dizziness. No other reactions have been noted. Administration of oxygen, barbiturates or stimulants was not required.

TECHNIC

The optimal dose has been found to be 10 cc. of 0.25 per cent tetracaine solution, given intravenously. The solution is administered slowly, over three to five minutes. The patient is kept supine during the infusion and for about five minutes afterward.

The 0.25 per cent solution is prepared by adding the contents of a 250 mg. ampul of tetracaine crystals to 100 cc. of isotonic sodium chloride solution. This solution can be kept in a rubber-stoppered bottle from which small amounts can be drawn as needed. The crystals should be dissolved in an isotonic solution rather than in distilled water. The injection can be conveniently made with a 25 gage needle, which causes only slight venous trauma and facilitates slow administration, although, of course, any needle suitable for intravenous use can be employed.

CLINICAL DATA

Tetracaine has been used intravenously in the present study in the treatment of arthritis, leprosy, muscle strain, lower back pain, asthma and miscellaneous conditions, such as hyperactive carotid sinus syndrome, pain in the chest and neuritis. Results are shown in the table. Of 104 patients treated, 98 or 94 per cent experienced definite improvement. Ages ranged from 15 to 80 years. Persons treated were Caucasian, Hawaiian, Negro, Filipino, Chinese, Korean, Japanese and Portuguese, and no difference in racial tolerance could be demonstrated. Most of the patients were workers on a sugar plantation seen in an

industrial medicine practice. Some were patients or staff members at the Kalaupapa Settlement, Molokai, Territory of Hawaii, the center for the treatment of leprosy in Hawaii.

The effects of tetracaine given intravenously are similar to those of intravenously administered procaine, but the action is more prolonged and the result more pronounced. Tetracaine apparently has an affinity for inflamed or traumatized tissues, as well as an antispasmodic action. Its administration gives good results in spastic conditions of both smooth and skeletal muscle as far as can be determined from the present study; spasm of skeletal muscle and bronchial spasm respond equally well to this treatment. In addition, tetracaine probably has an affinity for inflamed or hyperirritable nerves as shown by the good effects of its use in patients with hyperactive carotid sinus syndrome and

Summary of Results with Intravenous Administration of Tetracaine Hydrochloride

Conditions Treated	Total Patients	Total Doses	No. Patients Improved	No. Patients Not Improved
Asthma	11	22	11	0
Arthritis	20	38	19	1
Low back pain	18	35	16	2
Muscle strain	10	12	9	1
Leprosy	11	23	10	1
Miscellaneous				
Hyperactive carotid sinus syndrome	2	2	2	0
Pain in the chest	8	12	8	0
Neuritis	3	4	3	0
Pain, burns, etc.	2	2	2	0
Other	19	46	18	1
Totals	104	204	98	6

various neuritides. Chiefly, it relieves pain, probably by an anesthetic effect on the nerve endings in any painful area. An antihistaminic action can also be postulated, though no laboratory proof is available as yet. The circulation is improved in the affected area by local vascular dilatation. These actions will be more apparent on consideration of the various conditions treated.

ASTHMA

Eleven of the patients in this series were treated for asthmatic attacks. In all of them relief was immediate. One patient had not shown improvement after two doses of epinephrine, one intravenous injection of theophylline and inhalations of a mixture of helium and oxygen. He was finally given 10 cc. of 0.25 per cent tetracaine solution intravenously and was free of respiratory embarrassment almost immediately. All the patients treated liked the method. In those who were treated at different times for more than one attack, response was uniformly good. A total of twenty-two doses was given for asthma.

ARTHRITIS

In the treatment of the milder types of arthritis limited to one or two joints giving tetracaine intravenously has proved efficacious; 20 patients with arthritis received a total of thirty-eight doses, and the condition of 19 was improved. A 61 year old Portuguese man who had been a constant visitor to the clinic for many years, a sufferer from chronic rheumatoid arthritis, was completely relieved after five injections. However, in most patients the rheumatoid arthritis will probably respond better to large intravenous doses of procaine.

LEPROSY

While the average physician will not concern himself with the treatment of leprosy, it may be mentioned in passing that some of the minor complications of leprosy are benefited by the use of tetracaine. Eleven patients in this series were victims of leprosy. Five of these had intolerable itching, not relieved by treatment with antihistaminic drugs or other medicaments. These 5 reported cessation of itching, and in several relief lasted as long as four months. Two of the patients had such severe itching that only an alcoholic stupor would assuage their symptoms. Both were given 100 mg. of tetracaine in 500 cc. of isotonic sodium chloride solution. One felt better almost immediately. The other, seen a few hours after the infusion, complained that the itching had moved from his back to his arms. The infusion was repeated on the following day and the itching disappeared. All 5 of these patients complained of a "deep" itch which was not relieved by surface scratching. This itch was so severe that the patients would pound themselves or each other until the skin became pulpy over the "itching" area. The literature on leprosy contains no reference to this "deep" itch, but it is probably a form of neuritis of the larger nerve trunks, interpreted by the patients as itching.

The remaining patients with leprosy were treated for various painful conditions, such as arthritis and painful neuritis. Of the 11 patients treated, 10 reported satisfactory results. A total of twenty-eight doses was given in this group. Incidentally, almost all these 11 subjects had some damage to the liver, and, as far as could be ascertained, the tetracaine treatment had no adverse affect. Use of tetracaine gives only symptomatic relief of leprosy and has no effect on the course of the disease, to the best of my knowledge. Definite treatment of leprosy is best carried out with sulfone drugs.

PAIN IN THE LOWER PART OF THE BACK

Pain in the lower part of the back is one of the commonest complaints in a general or an industrial medicine practice. In all patients, gynecologic (in the female patient), urologic, orthopedic, neuritic and mechani-

cal causes should be ruled out. A great percentage of the patients with pain in the lower part of the back have no abnormal physical or roentgenologic findings. In many, the pain itself is the disease and no pathologic tissue changes can be found. The usual treatment consists of administration of acetylsalicylic acid, heat and liniment, use of adhesive strapping and reassurance. Many of these pains in the lower part of the back respond well to local injections of procaine in the painful areas, or in the trigger zones, if any exist. However, the results are equally good with tetracaine given intravenously and the procedure is quicker. Eighteen patients received a total of thirty-five injections; of these, 16 reported improvement and 2 had no relief. Patients receiving this drug made fewer visits to the clinic and returned to work more quickly than those treated in the conventional manner.

The following case report illustrates the efficacy of tetracaine treatment of pain in the lower part of the back.

C. T., a 56 year old Filipino male janitor, fell from a horse in July 1948. He reported severe pain in the left lower part of the back and in the posterior aspect of the left thigh. Roentgenograms of the spine showed no pathologic involvement. Myelograms were not done. Treatment consisted of use of salicylates, heat and liniment. Four months after the injury, he was still complaining of pain and on examination was noted to have stiffness of the left lower part of the back, spasm and anesthesia on the lateral aspect of the left thigh and hypoactive left patellar reflex. A provisional diagnosis of herniated lumbar intervertebral disk was made. For the purpose of giving temporary relief, 10 cc. of 0.25 per cent tetracaine solution was administered intravenously. The patient experienced immediate relief of pain. On the following day, examination showed that the spasm and anesthesia were no longer present. The patient was followed for a period of eight months after treatment and continued to be completely free of symptoms.

All but 2 of the patients treated expressed great satisfaction with the use of tetracaine and preferred it to such palliative measures as infra-red radiation, diathermy and administration of salicylates. The number of visits per patient for pain in the lower part of the back decreased strikingly after tetracaine injections were started. I have taken four intravenous injections of tetracaine for such pain caused by a chip fracture of one of the lumbar vertebrae; relief lasts from four to six months. In the treatment of primary pain in the lower part of the back intravenous administration of tetracaine seems to be more satisfactory than other methods. This is probably due not only to the direct action of the tetracaine molecule on the irritated nerve endings but to the spasmolytic and vasodilator effects of the drug.

MUSCLE STRAIN

Muscle strain of the upper and lower extremities often causes long-continued and disabling pain and stiffness. Ten patients were treated for muscle strain and 9 experienced relief. Whether the lesion is

myositis, fibrositis or calcific degeneration of muscle, relief is certainly afforded by this method. A total of thirteen doses was given. The condition in 1 patient was not improved and he preferred salicylates. The mode of action of tetracaine in this disorder is probably similar to that in pain in the lower part of the back.

MISCELLANEOUS

Thirty-four of the patients were treated for miscellaneous aches, neuritides and itching. These complaints ranged from pain in the chest following contusion to migraine headaches. Two patients had symptoms of hyperactive carotid sinus syndrome. They complained of dizziness and fainting on flexing or turning the neck and on bending forward. Pressure on the carotid sinus elicited the same symptoms. Each patient received one injection of tetracaine and had complete relief immediately. No recurrence was noted in either patient. This result suggests that the drug fixes itself to hyperirritable or inflamed nerve endings. Two of the patients had minor causalgia of several months' duration. The disease in both of them had been improved, but not completely relieved, by local nerve blocks; after intravenous administration of tetracaine the patients reported that the residual discomfort was so insignificant that they did not desire further treatment. However, without more conclusive evidence and further clinical trial, no statements can be made concerning the effect of tetracaine treatment on causalgia.

Two patients with migraine headaches were treated. One was seen on the third day of the attack and tetracaine was used along with other drugs. No conclusions could be drawn. The other patient had been subject to weekly migraine headaches and on two occasions the headaches were aborted at the onset by the administration of 10 cc. of tetracaine solution.

The remaining patients in this group were treated for painful scars, neuritis, itching, pleuritic pain and burns. Pleuritic pain in 6 patients was obtunded immediately. Itching was the chief complaint of 6 of the patients. One patient had Addison's disease; 1 had itching following a severe burn, and the other 4 had various dermatitides. In every patient the itching was relieved for periods of one to three days. It is believed that tetracaine is an ideal drug for the control of intractable itching. Of the 34 patients in this miscellaneous section, 33 were improved; the remaining 1 was a nurse with dysmenorrhea of three days' duration. Forty-eight doses were given in this group. Some of the patients had been treated for a time with salicylates, diathermy, infra-red radiation, liniment and other palliative procedures. After receiving tetracaine, most of them desired no further treatment. In the industrial medicine clinic, in which most of the tetracaine was used

for pain in the lower part of the back, muscle strain and miscellaneous pains, the number of visits per patient decreased notably in two months. This is propably due to the fact that tetracaine is a more definite treatment than the palliative procedures.

SUMMARY

One hundred and four patients have received a total of two hundred and four infusions of tetracaine hydrochloride intravenously for asthma, various pain syndromes, complications of leprosy and miscellaneous conditions. Toxicity has been minimal, consisting of slight nausea in 1 patient and syncope in 1 other, both of which were easily controlled. Most of the injections were of 10 cc. of 0.25 per cent solution, given slowly over a period of about three to five minutes. Twenty patients were treated for arthritis and 19 reported improvement. Eleven of the patients were treated for complications of leprosy and 10 were relieved of symptoms. Of 18 with pain in the lower part of the back, treatment was successful in all but 2. Muscle strain in various areas responded well in 9 of 10 patients. Eleven patients received tetracaine intravenously for asthmatic attacks and all 11 were freed of respiratory embarrassment. Thirty-four patients were given injections for miscellaneous neuritides, pain syndromes, minor causalgia and itching. Thirty-three of these needed no further treatment. In all the patients in whom this therapy was employed results were far superior to those obtained from palliation in the form of diathermy, massage, infra-red radiation and liniment. And in the over-all series it was noted that the number of visits per patient to the clinic decreased remarkably when tetracaine was used.

The actions of tetracaine when given intravenously are apparently antihistaminic, analgesic and antispasmodic. In addition, the drug seems to have a selective affinity for inflamed or traumatized tissue, concentrating in these areas. It also improves local circulation in the injured region, thus altering the pathophysiologic state. In addition, tetracaine may also act directly on hyperirritable or hypersensitive nerve tissue, as shown by its effect in the relief of hyperactive carotid sinus syndrome. This action, incidentally, has been used in preliminary work on psychiatric patients, which will be the subject of a later report.

The possibility of toxic reactions exists and must be remembered. Some patients are sensitive to tetracaine, although none has appeared in this small series. As with the administration of any local anesthetic, three possible untoward effects must be looked for: One is allergy, as just mentioned. Another is total vasomotor collapse, which has occurred following induction of nerve block and infiltration. The third is the typical reaction to local anesthetization, which is ushered in by convulsions and excitement, and which proceeds to medullary paralysis

and respiratory failure. If the solution is given rapidly, the danger is increased. It is axiomatic that a large dose of anesthetic can be given slowly with safety and that a small dose can cause trouble if given rapidly. In administering tetracaine intravenously, the patient should be watched carefully for any sign of untoward reaction and the injection should be made slowly. Any increased excitment, talkativeness, restlessness, muscular twitching, skin reaction or dyspnea is an indication for immediate cessation of treatment.

All the patients reported on in this paper were watched carefully during the injection, and all received the drug slowly. If these two precautions are taken and the possibility of toxicity is kept in mind, unwanted effects will be minimized.

42 North Dunlap (7).

FATTY CHANGE AND CIRRHOSIS OF THE LIVER IN PATIENTS WITH PANCREATIC LITHIASIS

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IN THE American medical literature of recent years, various authors have speculated on the relation in human beings of certain types of pancreatic disease to fatty change and portal cirrhosis of the liver.

In 1934 Zeckwer [1] cited the case of a senile nondiabetic patient with pancreatic lithiasis, producing obstructive parenchymal atrophy, in whom the liver showed fatty change. The patient suffered primarily from carcinoma of the esophagus.

Three years later Snell and Comfort,[2] with a detailed clinical description of 2 cases of pancreatic lithiasis and a brief summary of a third case, discussed the pancreaticohepatic relation. In the 2 patients whose cases were described in detail duodenal contents revealed an absence of pancreatic enzymes. There was enlargement of the liver with jaundice, ascites, steatorrhea and splenomegaly. The first patient was diabetic; he drank alcohol moderately; he improved on administration of lipocaic. The second patient did not have diabetes; he drank a good deal of alcohol; he improved with a high carbohydrate diet, intravenous administration of dextrose and mersalyl (salyrgan®). Snell and Comfort referred to the study of J. G. Mayo, in which, of 9 cases of pancreatic lithiasis coming to necropsy, there was some degree of fatty change in the liver in 3. They also referred to the postmortem descriptions of Choy and Oh [3] and of Paviot, Plauchu and Loras,[4] in whose cases pancreatic lithiasis was associated with an enlarged fatty liver.

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2. Snell, A. M., and Comfort, M. W.: Hepatic Lesions Presumably Secondary to Pancreatic Lithiasis and Atrophy: Report of 2 Cases, Am. J. Digest Dis. **4**:215-218 (June) 1937.

3. Choy, P. D., and Oh, H. Y.: A Case of Pancreatic Stone, China M. J. **45**:54-58 (Jan.) 1931.

4. Paviot, J.; Plauchu, M., and Loras, O.: Pancréatite scléro-kystique, suppurée chronique, accompagnée de lithiase pancréatique et de diabète: Gangrène pulmonaire terminale, Lyon méd. **155**:509-514 (April 28) 1935.

The patient of Choy and Oh had anemia, parasitic infection of the biliary tract and, perhaps, dietary deficiency. The patient of Paviot, Plauchu and Loras had diabetes mellitus, which was not controlled, and pancreatic suppuration.

In 1938 Roux [5] published clinical data on a male patient with pancreatic lithiasis who had an enlarged, presumably fatty, liver with ascites. Improvement occurred in the ascites when the patient received an active pancreatic extract. The patient did not have diabetes mellitus; he drank alcohol in excessive amounts.

In 1941 Snell and Comfort [6] recorded 3 additional cases of enlargement of the liver believed to be due to fatty changes in a series of 18 cases with pancreatic stones.

In 1946 Comfort, Gambill and Baggenstoss [7] reported the case of a 36 year old man with chronic relapsing pancreatitis, diabetes mellitus, steatorrhea and pancreatic calcification in which the liver enlarged and then receded in size on treatment. There was a history of alcoholism.

Besides pointing out the probable development of fatty metamorphosis of the liver in pancreatic lithiasis, Snell and Comfort,[2] with 1 personal case, mentioned the possibility of the progress of the fatty change into cirrhosis. Portal cirrhosis of the liver had been previously reported in pancreatic lithiasis by Fiessinger and Olivier,[8] Vallery-Radot and associates [9] and Witherspoon.[10] In two of these reports the patient gave a history of chronic alcoholism and poor dietary intake. Edmondson, Bullock and Mehl [11] found excess liver fat in 17 out of 26 cases of pancreatic stones studied post mortem. The fatty change was associated with alcoholism and/or cirrhosis in 15 cases and with diabetes in 1 case.

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5. Roux, J. C.: A propos d'un cas de lithiase pancréatique avec diarrhée graisseuse, ascite, et œdème: De l'adipose du foie consécutive à certaines lésions du pancréas, Arch. d. mal. de l'app. digestif **28**:527-532 (May) 1938.

6. Snell, A. M., and Comfort, M. W.: Incidence and Diagnosis of Pancreatic Lithiasis: Review of 18 Cases, Am. J. Digest Dis. **8**:237-243 (July) 1941.

7. Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: A Study of 29 Cases Without Associated Disease of the Biliary or Gastro-Intestinal Tract, Gastroenterology **4**:239-285 (April); 376-409 (May) 1946.

8. Fiessinger, N., and Olivier, H. R.: Sur un cas di lithiase du pancréas, Bull. et mém. Soc. méd. d. hôp de Paris **49**:1389-1391 (Nov. 27) 1933.

9. Vallery-Radot, P.; Miget, A., and Gauthier-Villars, P.: Lithiase et adipose du pancréas associées, Bull. et mém. Soc. méd. d. hôp de Paris **49**:1118-1123 (Oct. 30) 1933.

10. Witherspoon, J.: Pancreatic Lithiasis, South. M. J. **30**:1064-1067 (Nov.) 1937.

11. Bullock, W. K., and Edmondson, H. A.: Pancreatic Lithiasis and Calcification, California Med. **69**:104-108 (Aug.) 1948. Edmondson, H. A.; Bullock, W. K., and Mehl, J. A.: Chronic Pancreatitis and Lithiasis, Am. J. Path. **26**:37-55 (Jan.) 1950.

The appearance of fatty and cirrhotic changes in the liver has also been noted with primary pancreatic lesions other than lithiasis—for example, carcinoma, fibrosis, cysts, chronic and recurrent inflammation and congenital cystic fibrosis.

To the discussion of the relation of certain types of pancreatic diseases to fatty metamorphosis and portal cirrhosis of the liver, we add our clinicopathologic experience of the past seven years consisting of 7 cases of diffuse pancreatic lithiasis with fatty changes and cirrhosis of the liver.[12]

REPORT OF CASES

Group I. Fatty Changes; Cirrhosis (Hypertrophic Liver).—Case 1.—A. T., a 36 year old Negro woman, was admitted to the hospital for hematemesis Sept. 8, 1942. She died September 9.

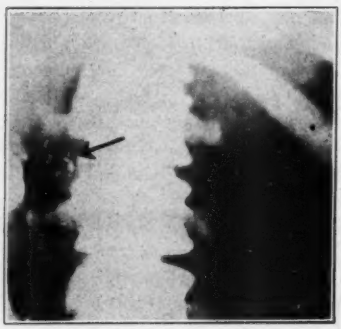

Fig. 1 (case 1).—Roentgenogram of the abdomen showing stones.

In 1927 the patient suffered an attack of jaundice with pain of one month's duration. At intervals from 1933 to 1935 she complained of abdominal pain, indigestion, emesis and constipation. In 1935, the urine contained no sugar; the blood glucose level was 121 mg. per hundred cubic centimeters. At this time an interligamentous cyst on the right side and a hydrosalpinx on the left were removed surgically.

In November 1937 the patient entered the hospital in diabetic coma. She responded to treatment with insulin and fluid. On recovery, she gave no history suggestive of diabetes mellitus. She still complained of abdominal pain. No abdominal organs were felt.

From December 1939 to May 1942 the patient was followed in the diabetic clinic with urine tests for sugar; the sugar in the urine was fairly well controlled by 200-80-80-calory diet. Her weight, however, decreased from June 1940. The parotid glands became swollen.

In May 1942 the patient entered the hospital for impending diabetic coma. She complained of pain in her back, fatigue and dyspnea. For several months she had

12. These include every case of diffuse pancreatic lithiasis which came to autopsy.

Fig. 2 (case 1).—Roentgenogram of the pancreas, in three gross sections post mortem showing stones.

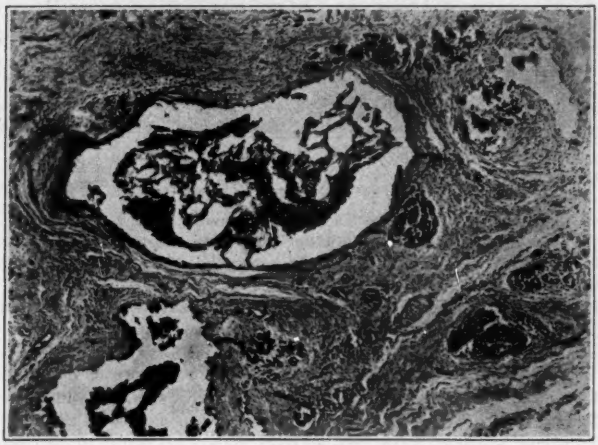

Fig. 3 (case 1).—Microscopic section of the pancreas, with dilated ducts, atrophic parenchyma and fibrosis.

had abundant white-yellow stools, ten times a day. The patient gave a history of drinking ½ to 1 pint (0.24 to 0.47 liter) of wine a day. On examination the parotid glands were swollen. The liver was palpable 4 fingerbreadths below the costal margin; it was smooth and tender; the spleen was not felt. There was no ascites. The hands showed "dermatitis." Roentgenograms revealed pancreatic calculi.

Under diabetic treatment, the patient gained 8 pounds (3.6 Kg.). The liver, however, did not recede in size. The patient was discharged June 1942, with a 180-70-70 calory diet and a daily dose of protamine zinc insulin of 70 units. From June to July urine specimens contained sugar (slight trace to 2 plus).

On September 8, the patient was admitted because of abdominal pain, hematemesis and jaundice. She had taken insulin regularly. The inferior edge

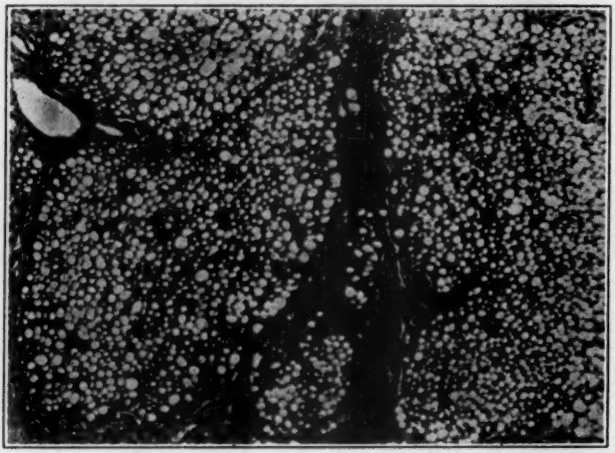

Fig. 4 (case 1).—Microscopic section of the liver, with diffuse fatty change and cirrhosis.

of the liver was palpated at the level of the umbilicus. The blood glucose level was 560 mg. per hundred cubic centimeters; the carbon dioxide-combining power, 17.2 volumes per cent. There was moderate anemia. Hematemesis and jaundice persisted. Coma and high fever supervened.

The postmortem diagnosis was diffuse pancreatic lithiasis with ductular obstruction and parenchymal atrophy and fibrosis; hypertrophic fat cirrhosis of the liver; esophageal varices; aspiration of gastric juice into the lungs; early pneumonia of the upper lobes; a small tuberculous nodule in the lower lobe of the left lung; swelling of the right parotid gland; status following pelvic operation with abdominal scar and peritoneal fibrous adhesions; interlobar fibrous pleurisy of the left lung; corpus luteum cyst, small uterine fibroid; early glomerulitis, and renal calcifications.

Gross Description of Pancreaticobiliary Hepatic Tract: No fluid was present in the peritoneal cavity. The liver weighed 2,800 Gm. The surface was finely granular; its consistency, firm, and its color, yellow. On cross section the liver showed loss of lobular markings and had a granular appearance. The gallbladder,

bile ducts, hepatic vein, hepatic artery and portal vein were not remarkable. The spleen weighed 220 Gm. Its consistency was reduced; it was red, and markings were not distinct. The pancreas weighed 25 Gm. It was firm and cut with a grating sound. On section parenchymal structure was lost. The ducts throughout the pancreas were dilated and filled with numerous small irregular yellow-white stones. Dilatation of ducts was most marked in the distal portion of the pancreas.

Microscopic Description of Liver and Pancreas: Liver. The capsule was slightly thickened. The normal liver architecture was not preserved. A pseudolobular pattern was present. The parenchymal cells showed tremendous fatty change with large vacuoles. Compressed liver cells remained at the periphery of the pseudolobules, which were surrounded by broad bands of connective tissue. There was moderate interstitial inflammation with infiltration of neutrophils and round cells. The bile ducts appeared increased in number. Slight evidences of jaundice were seen. No hyaline bodies in parenchymal cells were noted. Stains for iron revealed no significant amount of pigment.

Pancreas. The normal structure was not preserved. The ducts were markedly dilated. The lumens contained desquamated epithelium, debris, secretion and calculi. There was tremendous atrophy and disappearance of parenchyma. Fibrosis was marked. Interstitial inflammation was slight. Islets of Langerhans still remained. Arterial walls revealed slight hyaline thickening.

CASE 2.—B. K., a 58 year old white woman, was admitted to the hospital Oct. 31, 1945. She died November 12.

In 1936 the patient was first admitted to the hospital with complaints of recurring attacks of pain in the back and epigastrium. She also had bloating and distention of the abdomen, with frequent attacks of nausea and emesis. Vomiting eased the pain. The patient was bothered with increased thirst and constipation. She drank a bottle of beer a week. In 1935 a pelvic operation was performed in another hospital.

On examination, the upper part of the abdomen showed deep tenderness. The liver and spleen were not felt. The urine contained no sugar. Serial study of the gastrointestinal tract disclosed no significant abnormality.

On final admission, in 1945, the patient complained of pain in the right upper quadrant radiating to the shoulder and over the entire abdomen, persistent backache, anorexia, dysphagia, weakness, dyspnea, edema, epistaxis and jaundice. Examination disclosed that the patient was jaundiced and poorly nourished. The heart was enlarged. Rales were heard at the base of each lung. The liver was enlarged to percussion. Ascites was present. The ankles were edematous.

In the hospital, fever, chills and coma appeared terminally.

Laboratory studies revealed that the urine contained no sugar. The blood sugar level was 103 mg. and the hemoglobin level 5 Gm. per hundred cubic centimeters; the red blood cell count was 1,060,000 per cubic millimeter. The van den Bergh test showed a bilirubin content of 4.6 to 2.5 mg. per hundred cubic centimeters, and total protein content was 5.1 Gm. per hundred cubic centimeters. The blood culture yielded a growth of a hemolytic Staphylococcus aureus. In a plain roentgenogram of the abdomen, stones were not seen.

The postmortem diagnosis was diffuse pancreatic lithiasis with ductular obstruction and parenchymal atrophy and fibrosis; hypertrophic fat cirrhosis of the liver; jaundice; enlargement of the spleen (acute splenitis); acute meningitis; septicemia; ascites; bilateral hydrothorax; hydropericardium, diffuse pulmonary hyperemia and edema; hemorrhagic diathesis; anemia; fatty degeneration of myocardium; moderate hypertrophy of the left ventricle; cervical polyps; status following pelvic operation with abdominal scar and pelvic adhesions; fibrous adhesive pleurisy;

arteriosclerotic scarring of the kidneys with renal calcifications, and slight myocardial fibrosis.

Gross Description of Pancreaticobiliary Hepatic Tract: Ascites was present. The liver was enlarged. The right lobe measured 20 by 19 cm., and the left lobe, 23 by 13 cm. The surface was granular; the consistency, increased, and the color, yellow. On section, a granular appearance was seen. The gallbladder, bile ducts, hepatic artery, portal and hepatic veins were not remarkable. The spleen weighed 500 Gm. The capsule showed few adhesions. On section, markings were not evident; the parenchyma was mushy and friable. The pancreas could not be recognized as a definite organ. On gross section, the ducts throughout were dilated and contained small irregular stones. The parenchyma was atrophied and fibrotic. In the head of the pancreas only fat was found.

Microscopic Description of Liver and Pancreas: Liver. The capsule was slightly thickened. The normal structure was not preserved. Pseudolobules formed by fibrous tissue were present. The parenchymal cells were involved by tremendous fatty changes with large vacuoles. Interstitial inflammation, chiefly with infiltration of round cells, was distinct. Bile ducts appeared increased in number. The arterial walls were hyalinized. Liver cells contained brown pigment and disclosed regressive changes. Hyaline bodies were noted. Stains for iron revealed no significant amount of pigment.

Pancreas. The normal markings were not seen. The ducts were markedly dilated. The lumens contained laminated pink-staining material and calculi. The walls were thickened. There was marked atrophy of parenchyma, with fibrosis, interstitial inflammation and fatty infiltration. Islets of Langerhans were preserved. Arteries showed intimal thickening with hyalinization and reduplication of the elastic layer.

Case 3.—M. R., a 57 year old white woman, was admitted Sept. 21, 1948 for jaundice. She died September 28.

An accurate history could not be obtained. The following information was offered by relatives and by the patient in her lucid intervals. For the past two years she had had several attacks of "liver trouble." She had diarrhea about once a week, usually after meals. There was a history of emesis. The patient was said to have used sedatives, and she had taken "one shot of liquor" a night. For several weeks before admission to the hospital, she suffered with jaundice, nausea and emesis. She had eaten poorly.

On examination the patient was jaundiced and in an acutely ill state. The edges of the tongue were red. The liver was felt to the level of the umbilicus. The skin was dry and showed purpura. The ankles were edematous.

Laboratory studies showed that the urine contained albumin (1 plus) and no sugar. The hemoglobin level was 14 Gm.; the white blood cell count, 7,750 per cubic millimeter; the total protein content, 5.4 Gm. per hundred cubic centimeters (albumin 2.8 Gm., globulin 2.6 Gm.); the van den Bergh test showed a bilirubin content of 13.5 mg. per hundred cubic centimeters, and the alkaline phosphatase level was 3.8 Bodansky units. Needle biopsy of the liver showed "fat cirrhosis."

The postmortem diagnosis was diffuse pancreatic lithiasis with ductular obstruction and parenchymal atrophy and fibrosis; hypertrophic fat cirrhosis of the liver; chronic cholecystitis and cholelithiasis; generalized jaundice; bile nephrosis; hyperemia and edema of the lungs with acute pneumonia; acute splenitis, and a small leiomyoma of the uterus.

Gross Description of Pancreaticobiliary Hepatic Tract: No fluid was present in the peritoneal cavity. The liver weighed 2,400 Gm. The surface was finely

granular. On cross section the color was yellow. Lobular markings were replaced by pseudolobulations. The gallbladder was contracted, thickened and adherent. It contained four mixed stones, each about 1 cm. in diameter. The extrahepatic bile ducts were patent. The spleen weighed 140 Gm., and the pulp was friable. Markings were not visible. The pancreas was markedly decreased in size and fibrotic. The ducts were dilated and occluded by numerous small white stones.

Microscopic Description of Liver and Pancreas: Liver. The capsule was thin. The parenchyma showed tremendous fatty change. Cells in the peripheral zones were less vacuolated. In part, the lobular pattern still persisted. Periportal spaces were slightly thickened and inflamed with round cells and neutrophils. To a great part, the hepatic pattern was replaced by pseudolobulation through moderately thick bands of connective tissue issuing from periportal spaces. In certain areas bile ducts were increased in number. No hyaline bodies were noted. Besides fatty and cirrhotic changes, the liver displayed regressive change with jaundice.

Pancreas. The ducts were distinctly dilated. The lumens contained secretion and calculi, some in a laminated pattern. There were marked atrophy and disappearance of the parenchyma. Scattered islets of Langerhans were seen. The interstitial tissue showed marked fibrosis and slight chronic inflammation. No pigment was made out. Arteries were markedly thickened, with narrowing of the lumens, intimal fibrosis and reduplication and hyalinization of the internal elastic layer.

Group II. Fatty Change; Cirrhosis (Atrophic Liver).—CASE 4.—C. B., a 56 year old white man, was admitted to the hospital June 19, 1948. He died July 3.

In 1937 the patient was admitted to the hospital for knifelike precordial pain. No cardiac murmurs were heard. Blood pressure readings were 140 mm. systolic and 100 mm. diastolic. The abdomen was soft. The right forearm showed an old amputation. In the hospital the patient continued to have pain, and emesis developed. The urine was sugar free; the blood glucose level, 95 mg. per hundred cubic centimeters. The electrocardiogram indicated right ventricular hypertrophy, suggestive of sclerosis of the coronary artery.

On a second admission, in 1939, the patient complained of sharp epigastric pain radiating across the back to the precordium and left scapula, accompanied with vomiting. His appetite was good. Indigestion with periodic attacks of pain and with belching of gas had been present for six years. There was no history of jaundice. Bowel movements were regular, but there was morning emesis. The upper part of the abdomen was tender. The urine contained no sugar; the blood pressure was 140 mm. systolic and 70 mm. diastolic.

On final admission, the patient was transferred from another hospital because of pulmonary tuberculosis. He admitted that he was diabetic but did not require insulin. The urine contained sugar (4 plus). A roentgenogram of the chest revealed infiltration of the upper two thirds of the left lung, with cavitation, and infiltration of the upper two thirds of the right lung, of less marked degree. No masses were felt in the abdomen. The hemoglobin level was 81 per cent. On a 250-100-100 calory diet without insulin, the urine remained sugar free. The sputum contained acid-fast bacilli.

The postmortem diagnosis was bilateral chronic pulmonary tuberculosis with cavitation; bronchopneumonia, chronic fibrous adhesive pleurisy on the left side and calcific caseous tuberculosis of the tracheobronchial lymph nodes; diffuse pancreatic lithiasis with dilatation of ducts with infection and fibrosis; fatty change of

the liver with early cirrhosis in certain areas; scars from peptic ulcer in the prepyloric part of the stomach; a small ulcer of the colon; a small polyp of the sigmoid colon, and slight myocardial fibrosis.

Gross Description of Pancreaticobiliary Hepatic Tract: No fluid was present in the peritoneal cavity. The liver weighed 1,310 Gm. Its surface was smooth; its edge, blunt, and its consistency, doughy. The color was distinctly yellow. In certain areas, the cut surface showed pseudolobulation. The gallbladder, bile ducts, hepatic vessels and portal vein were not remarkable. The spleen weighed 190 Gm. Its capsule was thin and wrinkled. Follicles were not well seen. Trabeculae were prominent. The color was red, and the pulp was not friable. The pancreas was distinctly firm. It cut with a grating sound. On section, the ducts were dilated, with small stones, which were dark green, pale yellow and chalky white. Normal markings were largely replaced by fibrosis. In the head of the pancreas there was dilatation of a duct up to a cavity 2.5 by 1.5 cm. with granulation tissue in the walls. Culture showed a mixed infection.

Microscopic Description of Liver and Pancreas: Liver. The capsule revealed moderate hyaline thickening. For a great part the lobular pattern persisted. There was distinct fatty change, chiefly in peripheral parts of lobules. In parts, pseudolobulation was present because of marked fibrosis of the periportal spaces with extension into hepatic tissue. The thickened periportal spaces were moderately infiltrated with round cells and plasma cells. Bile ducts were increased in number. Vessels showed hyaline thickening, but hyaline bodies were not seen. Stains for iron revealed no significant amount of pigment.

Pancreas. In most sections the normal structure was lost. The parenchyma was largely replaced by fibrous and fatty tissue with inflammation. The acini which remained were atrophic. The ducts were dilated and contained inspissated secretion and concretions. The ductular walls were inflamed. The vessels were hyalinized. Islets of Langerhans were moderate in number and preserved in structure. In one section there was an old inflammatory focus with granulation and hemosiderosis in the wall.

Group III. Portal Cirrhosis;Only Slight Fatty Change.—CASE 5.—R. B., a 56 year old Negro, was admitted to the hospital Nov. 7, 1944. He died December 8.

The patient had been seen at intervals in the outpatient department from 1919 to 1941 for hypertension and arthritis.

In December 1941 the patient was first admitted to the hospital for an attack of severe cramplike epigastric pain which persisted day and night. He drank a glass of beer occasionally. On examination the patient was found to be poorly nourished; the heart was enlarged, and tenderness was elicited in the epigastrium. The liver and spleen were not palpable. The skin of the hands and legs was scaly. While in the hospital, the patient complained of abdominal pain and nausea. He had fever. His bowel movements were regular, but his stools were described as mucoid. Laboratory data were within normal limits. A roentgenogram of the abdomen showed mottled calcified shadows across the epigastrium in the position of the pancreas.

On final admission, in 1945, the patient complained of generalized aches, chilly sensations and cough. He also had dyspnea and edema of the ankles. He was emaciated. Rales were heard in the base of each lung. The heart was enlarged. The liver was palpable 2 fingerbreadths below the costal margin. The spleen was not felt. The ankles showed edema.

In the hospital the patient grew worse, with cough, fever, anemia and watery stools. Laboratory studies supplied the following data: The urine contained no

sugar; the van den Bergh test showed a bilirubin content of 6.5 mg. per hundred cubic centimeters. The prothrombin time was sixteen seconds (the control time was eleven seconds) and the Wassermann test elicited a negative reaction. The sputum did not contain tubercle bacilli.

The postmortem diagnosis was diffuse pancreatic lithiasis with ductular obstruction and suppuration, parenchymal atrophy and fibrosis; granular portal cirrhosis of the liver; calcific caseous tuberculosis of mediastinal, cervical and supraclavicular nodes; acute hematogenous tuberculosis of lung, liver, spleen and kidney; early nonspecific pneumonia and fibrinous pleuritis of the lower lobe of the right lung; fibrous pleurisy of the left lung; hypertrophy of the left ventricle with fibrosis, and chronic aortic valvulitis.

Gross Description of Pancreaticobiliary Hepatic Tract: No fluid was present in the peritoneal cavity. The liver weighed 1,540 Gm. The surface was finely granular; its consistency, increased, and its color, pale yellow. On section, lobular markings were not visible. Except for fibrous adhesions, the gallbladder was not

Fig. 5 (case 5).—Roentgenogram of the abdomen, showing stones across the upper part of the abdomen (barium sulfate in colon).

remarkable. The bile ducts, hepatic artery and hepatic and portal veins were patent. The spleen weighed 160 Gm. The surface revealed fibrinous exudate. On section tubercles were seen. The pancreas was atrophic and fibrosed. The ducts throughout were dilated, and they contained numerous irregular white stones and purulent exudate. Culture showed a mixed infection.

Microscopic Description of Liver and Pancreas: Liver. The capsule was somewhat thickened. The normal liver architecture was lost. Pseudolobules were present with interstitial inflammation and fibrosis. Liver cells and interstitial tissue contained a moderate amount of granular pigment which gave a positive reaction for iron. Moderate regressive changes had occurred. Some liver cells showed hyaline bodies. There was slight fatty change with large vacuoles in cells. Bile ducts appeared increased in number.

Pancreas. The ducts were markedly dilated. The epithelium was desquamated. Walls were inflamed with infiltration of round cells and plasma cells and were fibrosed. The lumens of some ducts contained calculi. There was extensive atrophy of the parenchyma. Only small islands of acini persisted. The intervening tissue

showed fibrosis, slight fatty infiltration, chronic inflammation and hemosiderosis. Fibrous tissue for the most part was dense and hyaline. Islets of Langerhans were seen. Vessels were moderately thickened.

CASE 6.—A. D., a 59 year old white man, was admitted to the hospital Oct. 2, 1946. He died October 25.

From 1934 to 1942 he had been treated for stricture of the urethra and extravasation of the urine, syphilis, fracture of the lumbar portion of the spine and incisional hernia.

In June 1946 the patient was admitted to the hospital for severe pain in the back which radiated down the legs. Other complaints included dyspnea and loss of weight. The patient drank a good deal of beer and whiskey; he ate well. The pain in the back was so severe that it disturbed sleep. A roentgenogram of the chest showed a mass lateral to the left hilus. No metastases were seen in the bones. The patient was discharged in August 1946, with a diagnosis of bronchogenic carcinoma, for which he refused operation.

On final admission, October 1946, a roentgenogram showed a density in the left hilus as before. The patient complained of pain in the chest, dyspnea and pain

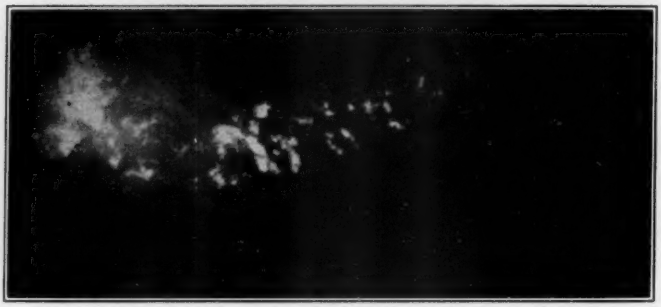

Fig. 6 (case 5).—Roentgenogram of the pancreas post mortem showing stones.

in the leg. He also had pain across the abdomen and frequent loose bowel movements. Sometimes the bowels were constipated. The liver was enlarged. Laboratory data included the following: The hemoglobin level was 80 per cent; the red blood cell count was 3,750,000 per cubic millimeter; the total protein content was 6.8 Gm. per hundred cubic centimeters, and the urine contained no sugar.

On the day before death, the patient's right arm became spastic and the left pupil larger than the right.

The postmortem diagnosis was bronchogenic carcinoma of the upper lobe of the left lung; metastasis to the right frontal lobe of the brain; confluent bronchopneumonia of both lower lobes; pulmonary emphysema of the upper lobes; fibrous adhesive pleurisy of the right side; diffuse pancreatic lithiasis with ductular obstruction and parenchymal atrophy and fibrosis; portal (Laennec's) cirrhosis of the liver; chronic cholecystitis; cholelithiasis and choledocholithiasis; syphilis of the aorta; arteriosclerosis of the aorta and the coronary arteries; renal arteriosclerosis; hyperplasia of the prostate gland; soft and friable spleen and renal calcifications.

Gross Description of Pancreaticobiliary Hepatic Tract: No fluid was present in the peritoneal cavity. The liver weighed 1,930 Gm. The surface was granular

and the consistency firm. On cross section, the surface was diffusely nodular. The gallbladder was fibrosed, small and adherent. It contained one mixed stone. One stone 0.6 cm. in diameter lay in the common bile duct 1.5 cm. above the ampulla. A stone 0.7 cm. in diameter was in the common hepatic duct. The hepatic artery and the hepatic and portal veins were patent. The pancreas was atrophied and fibrosed. The ducts throughout were dilated and contained numerous white calculi up to 0.7 cm. in diameter.

Microscopic Description of Liver and Pancreas: Liver. The capsule was slightly thickened with subcapsular infiltration of neutrophils. Pseudolobulation was present with increased connective tissue. There was moderate interstitial inflammation with neutrophils and round cells. Bile ducts appeared increased in number. A slight amount of fat was present. Arteries showed hyaline thickening. Stains for iron revealed no pigment.

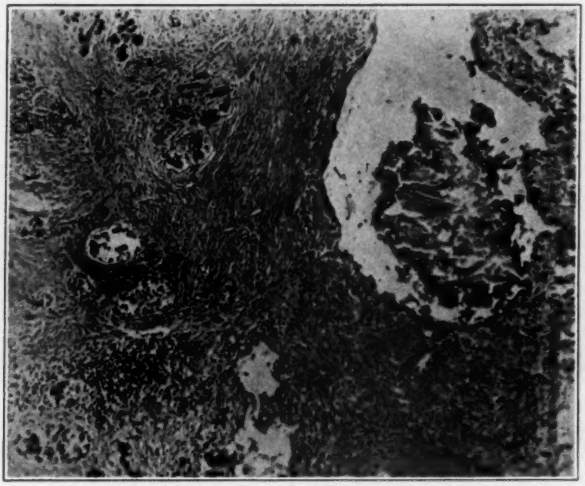

Fig. 7 (case 5).—Microscopic section of the pancreas, with stone, dilated duct, atrophic parenchyma, scattered islets, inflammation and fibrosis.

Pancreas. The normal structure was not preserved. The ducts were thickened. They were cystic with calculi and desquamated epithelium in the lumens. There was tremendous atrophy of parenchyma. Sections consisted chiefly of hyaline fibrous tissue. Islets of Langerhans remained; some were hyperplastic; others showed regressive changes. There was marked chronic interstitial inflammation. One vein revealed organized recanalized thrombosis.

CASE 7.—M. T., a 46 year old Negro woman, was admitted to the hospital Aug. 13, 1947. She died September 2.

In 1936 the patient entered the hospital for epigastric distress of one year's duration. She experienced a sense of fulness in the epigastrium with belching after meals. At frequent intervals sharp pains radiated to the back and right and left sides but never to the shoulders. Emesis occurred after meals. Bowel movements were regular. There was a loss of 7 pounds (3.2 Kg.) in weight.

Laboratory study showed the blood sugar content to be 94 mg. per hundred cubic centimeters; the van den Bergh test elicited normal results. Roentgenograms with use of dye disclosed no gallbladder shadow. A duodenal ulcer was diagnosed from serial gastrointestinal roentgen studies. Laparotomy was done, and the right fallopian tube and ovary were removed.

In 1940 the patient reentered the hospital for severe crampy, sometimes constant, pain in the epigastrium which radiated around both costal margins to the back. Emesis relieved the pain. The epigastrium was sore. During episodes of pain, the patient was constipated. Tenderness was elicited in both upper quadrants of the abdomen and the left lower quadrant. There was no jaundice.

Laboratory data showed the blood sugar content was 111 mg. per hundred cubic centimeters. At laparotomy no ulcer was found in the duodenum. The gall-

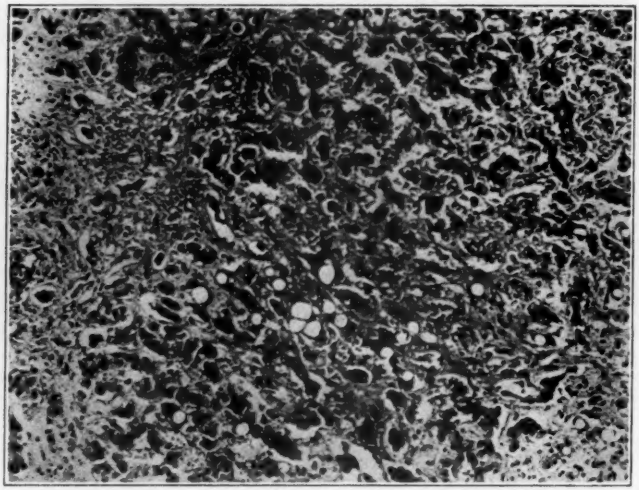

Fig. 8 (case 5).—Microscopic section of the liver, with slight fatty change and cirrhosis.

bladder was removed. The pathologist's report was chronic cholecystitis and cholelithiasis (solitary calculus 3 cm. in diameter).

In August 1943 the patient was brought to the hospital in diabetic coma. Her complaints had been headache, sharp radiating pain in the middle of the back, chills and fever. One examiner felt the edge of the liver. The blood sugar content was 329 mg. per hundred cubic centimeters. The patient responded to treatment and was discharged on a 150-70-60 calory diet. She was controlled in the diabetic clinic until she absconded.

In August 1946 the patient returned to the hospital with ascites and hematemesis. The liver was enlarged and irregular. The patient ingested three to four glasses of gin a night; the diet was said to be adequate. Laboratory data included the following: The urine contained no sugar; the blood glucose level was 95 mg. per hundred cubic centimeters; the hemoglobin level was 6 Gm.; the red blood cell count was 3,850,000 per cubic millimeter; the van den Bergh test showed a bilirubin

content of 7.2 to 2.5 mg. per hundred cubic centimeters; the cephalin flocculation reaction was 4 plus; the total protein content was 5.5 Gm. per hundred cubic centimeters, and the Wassermann test elicited a negative reaction. Needle biopsy of the liver was reported as showing Laennec's cirrhosis. The patient was discharged September 5.

On readmission, September 24, the complaints were dyspnea, nausea and emesis. The urine contained no sugar; the hemoglobin level was 9.2 Gm.; the red blood cell count, 2,900,000 per cubic millimeter. In June 1947 the urine contained no sugar; the blood glucose level was 266 mg. per hundred cubic centimeters.

On final admission the patient had convulsions, jaundice, fever, ascites, edema and coma. She was treated with plasma, whole blood and penicillin.

The postmortem diagnosis was diffuse pancreatic lithiasis with ductular dilatation and infection and parenchymal atrophy and fibrosis; portal (Laennec's) cirrhosis of the liver; ascites; jaundice; varices of the stomach with hemorrhages; bronchopneumonia of the upper and lower lobes of the right lung; absence of the gallbladder and the right tube and the ovary following previous operations, and fibrous omental adhesions.

Gross Description of Pancreaticobiliary Hepatic Tract: There was much ascites. The liver weighed 1,150 Gm. The surface was granular with atrophic areas; the consistency was firm, and the color, white-yellow. On cross section nodules ranged from 0.1 to 1 cm. in diameter. The gallbladder was absent. Bile ducts were slightly dilated. The hepatic artery and hepatic and portal veins were patent. The lesser sac showed extensive fibrous adhesions. The pancreas was atrophic, firm and white. The ducts were dilated and contained small white stones and green pus. No calcification was observed in the parenchyma.

Microscopic Description of Liver and Pancreas: Liver. The capsule was thickened, and its normal architecture was lost. Pseudolobules surrounded by hyaline fibrous tissue were present. The bile ducts appeared increased in number. There was interstitial inflammation with round cells and plasma cells. Jaundice was present, with pigment in liver cells and thrombi in bile canaliculi. In some areas, active regressive and inflammatory changes could be seen and slight fatty vacuolation. Hyaline bodies were noted. Stains for iron revealed no positive pigment.

Pancreas. The ducts were dilated, and their walls were thickened. The lumens contained desquamated epithelium and amorphous material. There was marked acinar atrophy with interstitial fibrosis, inflammation and fatty infiltration. The islets of Langerhans were preserved, and some appeared definitely hyperplastic. In some areas acini were still preserved but with extensive interstitial fibrosis.

COMMENT

Review of the literature raises the question: How shall the concept of the development of hepatic changes (fatty metamorphosis, fat cirrhosis and portal cirrhosis) in certain types of pancreatic disease, particularly lithiasis, be evaluated? For an answer, some authors have turned to data gained by the production of fatty liver and cirrhosis in animals through experiments on the pancreas.

When complete removal of the pancreas is carried out in dogs, the liver undergoes fatty change which regresses if the animals are treated with insulin and dietary measures. Frequently, despite continued therapy, the fatty liver recurs. The dogs weaken; they lose weight, and

anorexia, jaundice and sensitivity to insulin develop. Excretion of glucose diminishes. There is a decrease in the blood lipids and cholesterol esters. The chief postmortem finding depends apparently on the duration of survival. There may be fatty metamorphosis, fatty cirrhosis or portal cirrhosis of the liver. The occurrence of fat in the liver of depancreatized dogs is prevented by the use of raw beef pancreas, pancreatic extract, lecithin, choline, methionine and lipocaic. Furthermore, these substances slowly demobilize hepatic fat. Fatty liver in dogs can be produced also by fistula and ligation of the pancreatic duct, and it has been prevented or alleviated by the administration of pancreatic juice.[13]

In human beings may pancreatic insufficiency due to ductular obstruction or parenchymal destruction be the sole or primary pathogenetic factor for fatty change and cirrhosis of the liver? Snell and Comfort [2] intimated that the pathogenetic relation between pancreatic disease and fatty liver is probable, provided the pancreatic destruction and insufficiency is extensive enough and of proper duration. Sellers, Lucas and Best [14] stated on the basis of experimental evidence, "The clinician should therefore be on the look-out for signs of hepatic damage in cases of long-standing insufficiency of the external secretion of the pancreas." Cole and Howe [15] went so far as to describe a clinicopathologic entity for the pathogenetic relation under discussion and to designate this entity "the pancreaticohepatic syndrome."

In our 7 cases the pancreas was diffusely involved, apparently over a period of years, by lithiasis with ductular obstruction and by marked atrophy and fibrosis of the parenchyma. (We do not here discuss the cause and pathogenesis of the pancreatic lesions.) Pertinent to the question of the relation of chronic pancreatic disease to hepatic changes were the fatty change, fatty cirrhosis and portal cirrhosis of the liver. Undoubtedly the fatty cirrhosis in cases 1, 2, 3 and 4 originated with diffuse fatty metamorphosis. On the evidence of various clinical and pathologic investigations the possibility that the portal cirrhosis in cases 5, 6 and 7 was preceded by a fatty liver had to be considered but could not be decided absolutely.

At this point, the temptation might be great to correlate the findings in our cases with those in experimental animals in which fatty liver and cirrhosis develop after depancreatization or ligation of the pancreatic duct and to classify our cases under the title "the pancreatic syndrome."

13. Best, C. H.: Diabetes and Insulin and the Lipotropic Factors, American Lecture Series, no. 21; American Lectures in Physiology; Beaumont Foundation Lecture Series, no. 26, Springfield, Ill., Charles C Thomas, Publisher, 1948, pp. 23-40.

14. Sellers, E. A.; Lucas, C. C., and Best, C. H.: Lipotropic Factors in Experimental Cirrhosis, Brit. M. J. **1**:1061-1065 (June 5) 1948.

15. Cole, W. H., and Howe, J. S.: The Pancreatico-Hepatic Syndrome: Pancreatic Fibrosis and Fatty Liver, Surgery **8**:19-33 (July) 1940.

On further thought, however, we wonder how far we are justified in making such a correlation. Certain authors, though seeing a pancreaticohepatic relation, view it on a pathogenetic basis different from that previously described. Gillman [16] explained the relation on the basis of severe malnutrition with hepatic lesions preceding those in the pancreas. Others have related the fatty liver and cirrhosis to alcoholism, with which they also associate chronic recurring pancreatitis and lithiasis.

In assessing and classifying our cases—the second largest group of autopsy cases to be reported—we should like to use them to open the whole subject of the "pancreaticohepatic syndrome" to critical review. We start with an analysis of the cases reported from whatever pancreatic lesion. Only a small number have been described in the literature. Estimation of duodenal enzymes was but occasionally made. Complete chemical studies of the blood and stools were notably lacking. In some cases neither the pancreas nor the liver was observed through biopsy or autopsy. In cases in which the pancreas was examined, the involvement indicated a chronic progressive lesion. In animal experiments, depancreatization produces a rapid withdrawal from the duodenum and blood of the factor or factors possibly connected with production of fatty changes in the liver. In ductular ligation, although the pancreatic juice is excluded from the duodenum the excretory parenchyma remains for a period before marked atrophy results. Further, animal experiments are controlled in regard to insulin need and avoidance of infection. Although basal rations employed by various investigators have not been standardized, dietary measures are prescribed which ordinarily maintain a healthy dog. In human cases, reported with lithiasis (or with other pancreatic lesions), histories often contain notes of restricted diet, ingestion of alcohol, uncontrolled diabetes mellitus, infection, anemia, jejunocolic fistula and loss of weight, factors which in themselves may predispose to fatty change and cirrhosis of the liver. Hepatic response to certain lipotropic substances as demonstrated in human cases does not specifically prove a "pancreaticohepatic syndrome," because lipotropes may demobilize fat induced by different causes. Appreciable fatty changes in the human liver have not been described after operations necessitating ligation of the pancreatic duct or total pancreatectomy.

Continuing our critical review of the "pancreaticohepatic syndrome," we cannot escape analyzing our own cases in the light of the criteria that we have focused on those in the literature. In none were chemical determinations of duodenal content for pancreatic enzymes or of blood and stools for variations in fat and protein digestion and metabolism carried out. But in all, ductular obstruction, parenchymal atrophy and

16. Gillman, T., in discussion on Baggenstoss, A. H.: The Pancreas in Uremia, Am. J. Path. **23**:908-909 (Sept.) 1947.

fibrosis of the pancreas suggested deficiency of external secretion. In case 1 the clinical history indicated steatorrhea; in cases 3, 5 and 6 there was a history of loose or mucoid stools; in case 4, autopsy disclosed fatty stool in the colon. Factors which in themselves may possibly contribute to fatty changes and cirrhosis of the liver had to be thought of: diabetes mellitus (cases 1, 4 and 7); history of ingestion of alcohol (cases 1, 3, 6 and 7); possibly poor dietary intake—signs of undernourishment (cases 1, 3 and 5); hemosiderosis in the liver (case 4); pancreatic infection, and pulmonary tuberculosis (cases 4, 5 and 7); choledocholithiasis (case 6). It must be mentioned that in cases 1 and 2 the liver first became palpable years after the onset of the illness; in case 1 the liver did not recede in size when the diabetes was controlled; ingestion of alcohol was slight in case 3; hemosiderosis in case 4 was moderate, and pancreatic infection in cases 5 and 7 was slight to moderate.

Critical review, then, of the experimental and human data on "the pancreaticohepatic syndrome," including our own cases, leads to the following impressions: Experiments validate a fundamental relation between the pancreas and the liver in fat metabolism apparently dependent on an enzymatic basis in protein and lecithin digestion or, perhaps, on a "hormonal" basis. Although in human beings severe, prolonged pancreatic disease of obstructive and/or destructive type has been reported with fatty change and cirrhosis of the liver, the question arises how far and in what way the pancreaticohepatic relation can be interpreted. Is the relation as simple and obvious as some authors who have directly transposed the data on experimental animals to human cases believe?

In certain human cases (particularly those in which hepatic changes are associated with congenital cystic fibrosis of the pancreas and our case 2), within the limits of the clinical and laboratory data available, the pancreatic lesion seems to be the sole or the primary etiologic and pathogenetic factor for the hepatic changes. For these cases use of the term "pancreaticohepatic syndrome" in a strict and conclusive sense is justified.

In the majority of cases, however, the circumstances and sequences do not identically duplicate those in the dog with depancreatization or ductular ligation. The cases are involved from an etiologic and pathogenetic standpoint. Witness our cases 1, 3, 4, 5, 6 and 7. Multiple factors complicate consideration of the development of fatty liver and cirrhosis. The pancreatic factor—whether it is the sole, the primary, a contributory or a negligible factor—has to be measured against other factors which may play a part in the hepatic changes. In our cases 1, 3, 4, 5, 6 and 7, we cannot exclude the pancreatic lesion as a primary factor. Further, even if the hepatic changes were instigated by other causes—alcoholism, dietary deficiency, diabetes, infection—the pancreatic factor may still have accentuated them and prevented their recovery by inter-

fering with the liberation of lipotropic factors through digestion of food. For the involved human cases, unqualified use of the term "pancreaticohepatic syndrome" may be transposing the experimental data too freely and may be placing too facile an interpretation on the human data. The term, though, might be employed loosely for convenience of bringing together these involved and complex cases of fatty liver and cirrhosis associated with pancreatic disease so that they could be compared on the basis of their clinicopathologic findings and correlated with the present experimental data and those from future research. Each case should be evaluated clinically and pathologically for type, extent and duration of the pancreatic lesion. The onset and course of hepatic changes ought to be determined. Chemical studies of the duodenal content, stool, blood and liver, particularly in regard to the amount and type of fat, should be made. Further, all factors known to cause fatty liver and cirrhosis, occurring independently or accompanying the pancreatic factor, must be searched for and their possible influences estimated. Against these factors must be measured, finally, the pancreatic factor. Thus will the pancreaticohepatic relation in human beings become defined.

SUMMARY

In 7 patients with involvement of the pancreas by lithiasis, ductular obstruction, parenchymal atrophy and fibrosis the liver showed marked fatty change and/or portal cirrhosis. The possible relations between the pancreatic and the hepatic lesions are discussed on the basis of findings in the cases here reported, as well as on the basis of data in animal experiments and human cases reviewed from the literature.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1949

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TWO NEUROLOGISTS, in the broad sense of the word, received the Nobel Prize this year: A. Egas Moniz of Lisbon, Portugal, and W. R. Hess of Zurich, Switzerland. Egas Moniz first became known through his arteriographic studies of the brain. Then in 1935 he initiated the operation of frontal leukotomy. He had been in London at the International Neurological Congress and there heard Fulton report on his work with Jacobsen concerning the effects of frontal lobectomies on chimpanzees. One striking experiment showed that the removal of frontal cortex relieved agitation and anxiety. Egas Moniz returned to Lisbon and with his neurosurgeon, Lima, quickly put his ideas into action. The "leukotome" was devised and 20 patients underwent the operation of frontal leukotomy; 14 showed decided relief of agitated depression. The results were published in *Encéphale* in 1936. Freeman and Watts took up leukotomy in this country and "psychosurgeons" began work in various parts of the world. In August 1948 a congress was held in Lisbon to discuss frontal leukotomy and nearly 5,000 operations were reported. Now it is estimated that well over 11,000 leukotomies have been performed. Much suffering has been relieved; much information concerning the functions of the frontal areas of the cerebral cortex has been gathered. Seldom in the history of medicine has a laboratory observation been so quickly and dramatically translated into a therapeutic procedure.

The other Nobel laureate, W. R. Hess, of Zurich, is a professor of physiology and has been working steadily for twenty-five years at the problems of diencephalic function. He has mapped out and stimulated nuclei and tracts in the hypothalamus and brain stem, using new methods and adding greatly to the knowledge of this important area. Now he has published a monograph [1] of 187 pages which summarizes his life's work in one volume. There is much about autonomic function; there is even more about the effects on skeletal muscle, posture and expression of emotions. The experiments are especially important because many of

1. Hess, W. R.: Das Zwischenhirn: Syndrome, Lokalisationen, Funktionen, Basel, Switzerland, Benno Schwabe, 1949.

them were carried out with in-lying electrodes, so that stimulation was possible after the animal was completely recovered from the effects of anesthesia. The cats could walk freely about the laboratory with a light wire attached to the healed-in lead from the electrodes implanted in the brain. Remarkable photographs are shown of the effects of local stimulation on these practically normal cats.

One of the more controversial of Hess's accomplishments was the production of a state in cats that resembled sleep. It occurred with stimulation of the massa intermedia of the thalamus given at a slow rate for a relatively long period. These experiments have often been compared to those of Ranson,[2] but Ranson obtained his cataleptic effects in cats by making electrolytic lesions of a "wakefulness center" in the hypothalamus. Obviously, this was a quite different experiment. Both observations are important and are not contradictory. In other experiments Hess was able to produce ragelike states in cats by stimulating the posterior part of the hypothalamus.

RAGE REACTIONS

Reactions expressing anger in partially decorticated and decerebrate dogs and cats had been noticed by Goltz in 1892, but no special study of these phenomena was made until the work in Cannon's laboratory from 1925 to 1928.[3] Here Bard's experiments brought out the important point that successively larger and more caudal removals of the forebrain produced sham rage, until the level of the hypothalamus was reached. Then, if the posterior nuclei were destroyed, the symptoms of rage were practically eliminated, only a few poorly coordinated symptoms, such as piloreaction, lashing of the tail, growling and extension of the claws,[4] remaining in midbrain or decerebrate preparations. Thus, Bard established the fact that the nervous mechanism for the expression of the emotions was subcortical, and he placed the principal center for this motor integration in the posterior portion of the hypothalamus.

In the twenty years between Bard's paper in 1928 and the presentation of his experiments with Mountcastle at the 1947 meeting of the Association for Research in Nervous and Mental Disease, other pertinent

2. Ranson, S. W.: Functional and Clinical Significance of the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. **20**:342, 1940.

3. Cannon, W. B., and Britten, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XI. Pseudaffective Medulliadrenal Secretion, Am. J. Physiol. **72**:283, 1925. Bard, P.: Diencephalic Mechanism for Expression of Rage with Special Reference to Sympathetic Nervous System, ibid. **84**:490, 1928.

4. Macht, P., and Bard, P.: Studies on Decerebrate Cats in the Chronic State, Federation Proc. **1**:55, 1942. Keller, A. D.: Autonomic Discharges Elicited by Physiological Stimuli in Mid-Brain Preparations, Am. J. Physiol. **100**:576, 1932.

investigations have been made. In 1929, Fulton and Ingraham [5] showed that bilateral incisions into the base of the brain in front of the chiasm caused symptoms of sham rage. In 1940, Spiegel, Miller and Oppenheimer [6] caused partial attacks of sham rage by a similar lesion and also by a lesion of the hippocampus, fornix and stria terminalis. Wheatley [7] in 1944, by the aid of a stereotactic instrument, was able to make a focal lesion in the hypothalamus, leaving the posterior nuclei intact, but destroying the ventromedial nuclei. Some of these animals made a good show of coordinated rage reaction; others only partially exhibited the symptoms.

Bard and Mountcastle published in 1948 [8] their large and systematic series of experiments with chronic preparations. They studied the relation of neocortex to transitional cortex and archicortex, and of all these to emotional expression. The experiments give us a new concept of the mechanisms, and, although at present incomplete because final reports of the anatomic studies have not yet been made, they seem to offer an important key. The authors found it possible in cats to remove bilaterally the entire neocortex. Such a decorticate preparation shows no sign of anger, even when subjected to painful stimulation such as pinching the tail. If, however, in addition to decortication, the uncinate gyrus and amygdaloid region (archicortex) are injured bilaterally, an animal that previously showed pleasurable reactions immediately shows sham rage.

Besides all these ablation experiments, which by release of hypothalamic mechanisms allow sham rage to be elicited with great ease, there are experiments in which the various hypothalamic nuclei have been directly stimulated by implanted electrodes.[9] Hess's monograph gives descriptions of many such experiments. Experiments in Ranson's laboratory as early as 1933 demonstrated that partial rage reactions could be elicited by hypothalamic stimulation. Quite good exhibitions of sham rage were later elicited.

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5. Fulton, J. F., and Ingraham, F. D.: Emotional Disturbances Following Experimental Lesions of the Base of the Brain (Pre-Chiasmal), Am. J. Physiol. **90**:353, 1929.

6. Spiegel, E. A.; Miller, H. R., and Oppenheimer, M. J.: Forebrain and Rage Reactions, J. Neurophysiol. **3**:538, 1940.

7. Wheatley, M. D.: Hypothalamus and Affective Behavior in Cats, Arch. Neurol. & Psychiat. **52**:296 (Oct.) 1944.

8. Bard, P., and Mountcastle, V. B.: Some Forebrain Mechanisms Involved in Expression of Rage with Special Reference to Suppression of Angry Behavior, A. Research Nerv. & Ment. Dis., Proc. **27**:362, 1948.

9. (*a*) Masserman, J. H.: Effects of Sodium Amytal and Other Drugs on the Reactivity of the Hypothalamus of the Cat, Arch. Neurol. & Psychiat. **37**:617 (March) 1937. (*b*) Rioch, D. M., and Brenner, C.: Experiments on Corpus Striatum and Rhinencephalon, J. Comp. Neurol. **68**:491, 1938. (*c*) Hess, W. R.: Hypothalamische Adynamie, Helvet. Physiol. et Pharmacol. Acta **2**:137, 1944.

DOCILITY, SEXUALITY AND ORAL BEHAVIOR

A monkey without uncus, amygdala and anterior hippocampus,[10] or the orbital and insular parts of the mesocortex,[11] will be not only docile but devoid of fear. Many of them lick and sniff, and some have the most extraordinary tendency to explore everything with mouth and nose. Klüver and Bucy's monkeys would taste, mouth and nuzzle endlessly. Associated with this was sexual hyperexcitability, leading to excessive masturbation or indiscriminate and repeated sexual activity, if a partner, male or female, were available. Such behavior, produced in animals by operations on the brain, has far reaching psychologic implications.

It seems that the old brain (mesocortex and archicortex) is not just a "nose-brain" (rhinencephalon) for smell but a visceral brain, as MacLean[12] calls it. One of the unexplained discrepancies in all this new knowledge about emotion and the visceral brain is the difference in reaction between carnivora (dogs and cats) and primate (monkeys and man). No one has so far produced sham rage in a monkey and the clinical phenomena seen in man do not closely resemble it. On the other hand, the docile, placid state described by Bard in cats had been produced to some extent by Klüver and Bucy in their remarkable series of experiments on monkeys in 1939. Bard has made wild macaques tame by limited operations on the amygdaloid region.

At the 1949 meeting of the American Neurological Association, three papers were read that had important bearing on the problem of the functions of the old visceral brain (mesocortex and archicortex) as contrasted with the new discriminative and, in man, verbal cortex (neocortex). Operations on baboons in Fulton's laboratory[11] that removed the orbital part of the frontal cortex, the anterior insular cortex, the uncus and amygdaloid region caused compulsive oral investigation of all objects, whether food or nonfood—even sharp instruments and burning matches—accompanied with a more general loss of fear, but with no impairment of performance of simple visual discriminations.

Smith showed that when the anterior part of the cingulum is removed, monkeys show "tameness"[13] and loss of "social conscience." They have

10. Klüver, H., and Bucy, P. C.: Preliminary Analysis of Functions of the Temporal Lobes in Monkeys, Arch. Neurol. & Psychiat. **42**:979 (Dec.) 1939.

11. Fulton, J.; Pribram, K. H.; Stevenson, J. A. F., and Wall, P.: Interrelations Between Orbital Gyrus, Insula, Temporal Tip and Anterior Cingulates, Tr. Am. Neurol. A. **74**:175, 1949.

12. MacLean, P. D.: Psychosomatic Disease and the "Visceral Brain": An Elaboration and Speculation on the Papez Mechanism of Emotion, Psychosom. Med. **11**:339, 1949.

13. Smith, W. K.: Studies on the Cingular and Pyriform Regions of the Cerebral Cortex, Tr. Am. Neurol. A. **74**:169, 1949.

no fear and seem to have lost realization of the probable results of acts such as eating out of another monkey's hand. They are not ready for the reprisal. In short, they have some of the characteristics shown by monkeys with ablation of the uncus and amygdaloid region. This fits in with experiments that have shown [5] that the anterior commissure sends most of its fibers to the hippocampal region of both sides. Stimulation of this bundle causes sniffing, licking and chewing, and removal of the neocortex seems to release these reactions from higher control. These facts support Brodal's [14] conception of the hippocampus as an association center of the archicortex, and his statement that smell is to be looked on as only one of the several components of hippocampal function.

The cingulum is a link in this mechanism that connects with higher levels. It is mesocortex and merges at its borders into the neocortex near the sensory, motor and premotor areas. For years it has been generally thought of as olfactory in function. Stimulation experiments have shown that it has important suppressor and autonomic functions. Certain parts of the anterior cingulate cortex when stimulated in the monkey [15] produce a profound inhibitory effect on all muscular movements, with decided relaxation of the muscles. This is like the *"Adynamie"* reported by Hess [9c] from hypothalamic stimulation. Other areas in the anterior part of the cingulum produce facial movements, vocalization or changes in respiration and blood pressure, pupillary dilation and piloerection. Posteriorly, micturition is affected. The inhibitory effects on the cortex take place by way of the caudate nucleus, and the profound inhibition of skeletal muscles seems to be mediated by a large tract to the bulbar reticular formation.

Since the cingulum is highly developed in primates, in which smell is poorly developed, it seems obvious that the main function of the cingulum is not olfactory. The recent experiments substantiate this and suggest that this area is a dominant factor in autonomic control and is important for motor suppression. One is impressed with the possibility that here may be the mechanism which causes immobility under sudden emotion, with active visceral disturbances, vomiting, fainting, urinating and the like. Fulton [11] expresses the belief that the orbital areas of the frontal cortex are closely connected anatomically and functionally with the anterior part of the cingulum. Recent experiments in his laboratory

14. Brodal, A.: The Hippocampus and the Sense of Smell, Brain **70**:212, 1947.

15. Ward, A. A., Jr.: Anterior Cingulate Gyrus and Personality, A. Research Nerv. & Ment. Dis., Proc. **27**:438, 1948. McCulloch, W. S.: Cortico-Cortical Connections, in Bucy, P. C.: Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol. 4, p. 211. Smith, W. K.: Results of Ablation of the Cingular Region of the Cerebral Cortex, Federation Proc. **3**:42, 1944.

substantiate this. Stimulation experiments on man [16] corroborate the findings.

To summarize this mass of experimental data is difficult at present. To generalize from it is dangerous because many points are not settled. Nevertheless, a tentative formulation can be proposed. It would seem that in cats taking away the neocortex but sparing the mesocortex and archicortex leaves them docile, refractory to noxious stimuli and somewhat overready to react to pleasurable stimulation by showing affection. If some of the hippocampus is removed, this affability is increased. Sham rage does not appear until the uncus region is injured, i. e., the cortex of the uncinate gyrus, the amygdaloid nucleus and the tracts to the posterior part of the hypothalamus. Then the docile animal is turned into a furious one.

In monkeys no operation produces the sham rage reactions. Operations removing the uncus region (with parts of the hippocampal orbital and insular cortex, in some cases) cause some of the monkeys not only to be docile like the cats but to be devoid of fear, to have a strong tendency to explore everything orally and to have excessive sexual reactions. This combination of "oral tendencies" and sexual excesses fits in remarkably well with the observations of child psychiatrists. They note that the nursing child not only gets its first feelings of support and love through sucking at the breast but also shows pleasure which is known to be reciprocated by the mother. Thus, the earliest pleasures of feeding and sucking are associated with love and security. Later in life, when genital sexuality arises, the mouth and nipple may remain as erotic zones, for arousing sexual desire. The relationship psychologically is shown by the development of the normal infant. Clinically, it has been observed that excessive oral desires and dependence on the mother can lead to gluttony. Hunger in the infant causes great insecurity and rage reactions. Psychiatric evidence is abundant [17] that perpetuation of these infantile reactions in adult life may lead to nutritional and sexual disorders, such as food faddism, anorexia or obesity, masochism or sadism.

It is suggested by MacLean [12] that the inhibitory function of the uncus region is a mechanism by which "the frontal lobes stand guard" and repress fantasies and acts which are considered perverse. It represses those longings to lick, suck and bite in a primitive way, to release sex urges and to express rage. If the inhibition were not heeded,

16. Pool, J. L., and Ransohoff, J.: Autonomic Effects on Stimulating the Rostral Portion of the Cingulate Gyri in Man, Tr. Am. Neurol. A. **74**:172, 1949.

17. Alexander, F.; French, T. M., and others: Studies in Psychosomatic Medicine: An Approach to the Cause and Treatment of Vegetative Disturbances, New York, Ronald Press Company, 1948.

primitive feelings of guilt might arise. This is speculative. But at least here is a neurologic configuration in which such reactions might well take place.

The difference in reaction between carnivora (cats), who become furious when the amygdaloid region is removed, and primates (monkeys), who become placid, fearless and excessively sexual, is striking and unexplained. More experiments with different species will have to be performed before the answer is known. In the meanwhile one might speculate that for carnivorous animals a ragelike reaction is a necessity in procuring food. They have to kill to get their meat. They are mostly lonely hunters. In monkeys, on the other hand, one deals with a gregarious, socialized animal who is omnivorous and largely vegetarian. A rage reaction connected with picking a banana would be inept and worse than useless. This is well illustrated by Kohler's picture [18] of a group of chimpanzees working together to reach a banana. The rage reaction of the cat is connected with the visceral brain, smell, taste and alimentation both anatomically and functionally. Rage reactions in the monkey may only be related to defense and, therefore, are not aroused by lesions of the visceral brain.[19]

HYPOTHALAMUS AND PITUITARY

Since the first work on the ductless glands by Claude Bernard a hundred years ago, and the experiments of that strange genius, Brown-Séquard, the profession and the public have been expecting great things to come to psychiatry from endocrinology. Up to the present, few of these hopes have been realized; cretinism and hypothyroidism, mongoloid idiocy and pituitary disorders have quite definite relationships. But the great problems of psychiatry, schizophrenia, manic-depressive disorders and neuroses, have not been helped much by endocrinology. Hoskins has summarized two decades of work on the physiology of schizophrenia in his recent book.[20] Much spade work was done, but no clear picture emerged. Caspersson [21] brought evidence from the histologic laboratory that schizophrenia might be a metabolic disease. Now evidence seems to be coming from several sources that the pituitary and adrenocortical

18. Yerkes, R. M., and Yerkes, A. W.: The Great Apes: A Study of Anthropoid Life, New Haven, Conn., Yale University Press, 1929.

19. Cobb, S.: Emotions and Clinical Medicine, New York, W. W. Norton & Company, to be published.

20. Hoskins, R. G.: Biology of Schizophrenia, New York, W. W. Norton & Company, 1946.

21. Caspersson, T. O.: Cell Functions and Cell Growth in Normal and Pathological Conditions Studied by Quantitative Cytochemical Procedures, New York, W. W. Norton & Company, 1950.

hormones may be important in manic-depressive psychosis and schizophrenia. The great question is how the brain stimulates these glands through the hypothalamus.

The hypothalamus had its day of popular notoriety as the "seat of the emotions," where primitive emotions had their origin. It was even considered to be the habitation of the freudian "id." Such naïve interpretations of hypothalamic function are happily outdated. Today, one thinks of this group of nuclei as the center for the integration of the motor impulses of emotional expression and as the head ganglion of the autonomic nervous system. It is important to remember that the hypothalamus is the main outlet for neural messages from the primitive archicortex to the striated muscles, smooth muscles and glands. Thus, it has control over homeostasis and other autonomic functions. Probably no nerve pathways run directly from neocortex to hypothalamus, but it receives large and direct tracts from the archicortex (visceral brain).

Nerve fibers leaving the hypothalamus have important effects on the endocrine glands: (*a*) by a direct tract to the posterior part of the pituitary and (*b*) by relays down the brain stem and cord to the adrenal medulla. The hypothalamus discharges not only downward into the midbrain, hindbrain and cord for motor and glandular expression but upward into the thalamus with relays to the archicortex for visceral feelings and emotional stimulation; there are also relays to the neocortex for the maintenance of a state of alert wakefulness.

There is good evidence that cells in the central nervous system of fish and amphibians have a secretory function. Somewhat similar cells are found in the supraoptic and paraventricular nuclei of the mammalian hypothalamus which present many of the characteristics of secretory cells.[22] They have a special relation to the blood vessels. Some cells are penetrated by capillaries. The nuclei have an extraordinarily rich capillary network.[23] It seems possible, therefore, that these nuclei not only transmit nerve impulses but secrete hormones.

Recent work by Hume [24] indicates that the stimulation of secretions of the anterior portion of the pituitary from the hypothalamus is hormonal and does not depend on either nerves or a special venous portal system. The latter may be present and act as an adjuvant, but the

22. Scharrer, E., and Scharrer, B.: Secretory Cells Within the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. **20**:170, 1940.

23. Finley, K. H.: Angio-Architecture of the Hypothalamus and Its Peculiarities, A. Research Nerv. & Ment. Dis., Proc. **20**:286, 1940. Craigie, E. H.: Measurements of Vascularity in Some Hypothalamic Nuclei of the Albino Rat, ibid. **20**:310, 1940.

24. Hume, D. M.: Role of the Hypothalamus in the Pituitary-Adrenal Cortical Response to Stress, J. Clin. Investigation **28**:790, 1949.

25. Footnote deleted by author.

main stimulation seems to come from hypothalamic hormones reaching the anterior part of the pituitary by way of the general circulation. This is the best answer to date to that all-important question: How do emotions exert an effect on the endocrine system? Cannon, Ranson, Hess, Gellhorn and others in the past thirty years have given the answer as far as the adrenal medulla and the autonomic nervous systems are concerned. Now we are coming to grips with the adrenal cortex and the adrenocorticotropic hormones of the anterior portion of the pituitary (ACTH).

The recent use of this substance for the treatment of various systemic diseases, notably arthritis, has shown that it has a striking effect on the mental attitude of the patient and may precipitate changes of mood and of behavior that sometimes reach pathologic degree. This in itself is of interest and gives a clue to the possible origin of some mental symptoms. It also fits in with the theory of Altschule [26] that electric shock brings about its salutary effects not by direct action on frontal nerve cells but by the setting up of changes in the secretions of the endocrine system. He has shown that shock therapy causes an initial stimulation of the production of the sugar-active hormones, of the electrolyte-regulating hormone and of androgen. As treatment is continued, the response of the sugar-active hormones decreases and with it 17-ketosteroid excretion. The increase of the electrolyte-regulating hormone persists.

In studying patients with chronic schizophrenia, manic-depressive reactions and involutional melancholia, Altschule and his co-workers [26] found the most usual endocrine picture to be increased sugar-active hormone, approximately normal androgen and decreased electrolyte-regulating hormone. They found only one difference in the response of their psychotic patients to injection of ACTH from the response of normal controls. This was an abnormally great change in carbohydrate metabolism.

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26. (*a*) Altschule, M. D.: Physiologic Observations in Mental Disease, Bull. New England M. Center **11**:229, 1949. (*b*) Altschule, M. D., and Tillotson, K. J.: Effect of Electroconvulsive Therapy on Water Metabolism in Psychotic Patients, Am. J. Psychiat. **105**:829, 1949. (*c*) Altschule, M. D.; Parkhurst, B. H., and Tillotson, K. J.: Decreases in Blood Eosinophilic Leukocytes After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**:440, 1949. (*d*) Altschule, M. D.; Ascoli, I., and Tillotson, K. J.: Extracellular Fluid and Plasma Volumes in Depressed Patients Given Electric Shock Therapy, Arch. Neurol. & Psychiat. **62**:618 (Nov.) 1949. (*e*) Altschule, M. D.; Altschule, L. H., and Tillotson, K. J.: Changes in Leukocytes of the Blood in Man After Electrically Induced Convulsions, ibid. **62**:624 (Nov.) 1949.

27. Footnote deleted by author.

The work of Pincus, Hoagland, Hoskins and others [28] in Worcester, Mass., presents evidence that the adrenal cortex of psychotic patients is less responsive than that of normal persons to injections of ACTH. They subjected 34 psychotic patients to tests that caused acute stress and compared the results with previous work on control subjects. The increase in 17-ketosteroids found in normal controls did not appear in schizophrenic patients; the stress-induced lymphocytopenia did not occur in the patients; lymphocytopenia caused by administration of glucose appeared less in the patients than in the controls. The authors state their belief that a form of hypoadrenalism is present in the schizophrenic patients. They also found an abnormal ratio between androgens and estrogens in the schizophrenic group. The androgen to estrogen ratio in normal women was 1:23; in men of the control group it was 1:163, and in the male schizophrenic patients it was 1:97.

Altschule [28a] did not find these differences in his patients and suggests that they might be due to some type of depletion. More work is needed, but it seems as though the investigators are approaching an important area that may connect Hoskins' years of spade work [20] with the newer understanding made possible by the advances in chemical knowledge of the adrenocortical hormones [28] and the effects of stress as described by Selye.[29]

HEREDITY

Many endocrine disorders are strongly inherited and the possible relation of schizophrenia and manic-depressive reaction to the adrenocortical hormones brings up the much discussed question of the importance of the hereditary factor in these two mental diseases. Lack of definitive diagnostic methods makes it difficult to study the inheritance of these diseases. It is much easier in the neurologic field where the signs and symptoms are easier to see. For example, dystrophia myotonica is said by Thomasen [30] to be a "disturbance in the hypothalamus-hypophysis system," and the neurologic syndrome of this disease is so characteristic that it was chosen for particular study at the Institute for Human Genetics, in Copenhagen, Denmark. In this study Thomasen

28. Pincus, G.; Hoagland, H.; Freeman, H.; Elmadjian, F., and Romanoff, A. B.: A Study of Pituitary-Adrenocortical Function in Normal and Psychotic Men, Psychosom. Med. **11**:74, 1949. Hoskins, R. G., and Pincus, G.: Sex Hormone Relationship in Schizophrenic Men, ibid. **11**:102, 1949. Pincus, G.; Schenker, V.; Elmadjian, F., and Hoagland, H.: Responsivity of Schizophrenic Men to Pituitary Adrenocorticotrophin, ibid. **11**:146, 1949. Pincus, G.; Hoagland, H.; Freeman, H., and Elmadjian, F.: Adrenal Function in Mental Disease, Recent Prog. Hormone Research **4**:291, 1949.

29. Selye, H.: Textbook of Endocrinology, Montreal, Acta Endocrinol., University of Montreal, 1947.

30. Thomasen, E.: Myotonia, Aarhus, Denmark, Universitetsforlaget i Aarhus, 1948.

also included myotonia and paramyotonia, which are less common and perhaps are better considered as symptoms rather than diseases. Myotonia is part of the syndrome of dystrophia myotonica, which is clinically a combination of muscular dystrophy (mostly of the face, neck and shoulder girdle), myotonia, alopecia, cataract and endocrine disturbances. Gonadal degeneration occurred in 86 per cent of the male patients; reduced basal metabolic rate and colloidal degeneration of the thyroid were common. Mental deterioration is an important part of the picture. The author found 101 patients in 21 families and was able to trace the heredity satisfactorily in 18 of these. Denmark with its homogeneous population and good medical reporting is especially adapted to this work. The disease is inherited as a dominant. A large number of the adults are unmarried and the disease seems to eliminate itself by the impotence of the severely affected.

In myotonia the only symptom may be the lack of ability to relax muscles quickly after contraction; but muscular hypertrophy may be conspicuous. The disease is not common; 29 patients were located in 5 families. It is inherited as a simple dominant factor. Paramyotonia is a subspecies in which exposure to cold brings on a sustained contraction of the muscles, followed by more or less pronounced paresis. Muscular hypertrophy is a common concomitant. These diseases are striking examples of the complexity of the heredity when chemical, endocrine and mental disorders are all involved. Thomasen states he does not believe that these three disorders are genetically identical, but it would seem that he has not clearly understood the point of view of the authors [31] who have held that dystrophia myotonica is caused by the simultaneous combination of several genetic unit characters, whereas myotonia alone may be caused by a single unit character. Basically, the inherited disturbances are probably chemical and mediated by the endocrine glands.

Another important piece of work on inheritance comes from the Caroline Institute, in Stockholm, Sweden. This is a monograph by Prof. Sjögren and his colleague Dr Larsson on "Microphthalmos and Anophthalmos With or Without Coincident Oligophrenia." [32] Here the facilities of a well ordered Scandinavian state are again shown to be important for locating and following up the patients. A careful survey revealed 137 persons with the disorders in Sweden, 58 with feeblemindedness. Of the latter, 28 per cent were epileptic and 24 per cent had cataracts.

31. Cobb, S.: Foundations of Neuropsychiatry, ed. 4, Baltimore, Williams and Wilkins Company, 1947.

32. Sjögren, T., and Larsson, T.: Microphthalmos and Anophthalmos With or Without Coincident Oligophrenia, Copenhagen, Denmark, Ejnar Munksgaards Forlag, 1949.

No less than 71 per cent showed skeletal abnormalities, such as clubfoot and kyphosis. Some connection may be found with cases of spastic diplegia and hereditary ataxia. Toxoplasmosis, syphilis and rubella as causes were ruled out. The mode of inheritance is partially sex-linked recessive. It was believed that the material could be considered a complete inventory of these diseases in Sweden, so the figures can be used as an index for other populations. The careful geographic work showing the location of nests of the disease on certain islands is especially interesting. It is this sort of careful genetic work that will some day give to medicine the key to the great problems of heredity in the common neuropsychiatric disorders.

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Book Reviews

Contribucion del coeficiente citologico a la fisiología y patología de la correlación hipofisotiroidea. By Estanislao del Conte. Pp. 87 with 34 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

The book represents a summary of the author's own work on the pituitary-thyroid axis. After a renumeration of some cytologic problems dealing with secretory phenomena of the thyroid gland, the Altman freezing and drying method of fixation, together with a description of apparatus and a few modifications thereof, is described. The formation of intracellular colloidal droplets was taken as the cytologic criterion for stimulation of the thyroid cell after administration of thyrotropin. Other criteria, such as clear vacuoles and chromophobic colloid, were considered artefacts.

Observations on the intracellular colloid were made on normal and on hypophysectomized frogs and rats and on normal guinea pigs and chicks. For use in assay, a cytologic coefficient was devised. The cytologic coefficient was defined as a number obtained by dividing the observed number of intracellular colloid droplets per follicle by the mean follicular diameter in millimeters. A series of doses of thyrotropin was tested, and the results indicated a direct proportionality between the dose of hormone and the biologic effect in the thyroid as indicated by the coefficient. The sensitivity of this method for assay of thyrotropin was apparently great, since 0.0002 Junkman-Schoeller unit could be detected. High specificity was also claimed for this method, although nonhypophysectomized guinea pigs were used and experimental data dealing with specificity (comparable to those published by Dvoskin in this country) were not given.

The remainder of the book is devoted to clinical aspects of thyrotropic assays. The review of the literature in this field is adequate and detailed. The author found that serum (2 cc.) of normal persons did not give a thyrotropic response. Extraction of the serum by Fellinger's method, however, yielded thyrotropic responses for the reason, as the author states, that extraction removes any serum thyroxine which would inhibit the action of thyrotropin. It is interesting to note that the Australian workers have shown that the concomitant administration of thyroxine does not interfere with the response of the thyroid gland of the guinea pig to thyrotropin. The method for testing clinical material consists of injecting the extract equivalent to 2 cc. of serum into guinea pigs and determining the cytologic coefficient thirty minutes after injection. Various clinical entities were tested. The serum of normal persons gave a coefficient of from 40 to 60. Patients with exophthalmic goiter had coefficients of 15 or less, a negative value. Patients with exophthalmic goiter who had been successfully treated with antithyroid drugs or by subtotal thyroidectomy had coefficients of 40, the same as normal persons. Patients with exophthalmos and those having primary myxedema had coefficients as high as 100 to 150. Those with myxedema of pituitary origin had values of 15 or less, suggesting the absence of thyrotropin in the blood.

As a whole, the author's work suffers from lack of sufficient numbers of subjects for observation. There were, in all, 21 subjects, distributed as follows: 5 normal persons, 6 patients with untreated exophthalmic goiter, 2 with treated exophthalmic goiter, 2 with myxedema, 3 with exophthalmos, 1 with a hyperfunctioning pituitary lesion, 1 with myxedema of secondary origin and 1 with Cushing's disease.

The major conclusion is the same as that reached by others—that in exophthalmic goiter the excess thyroid hormone produced inhibits production of thyrotropin and that in myxedema excess thyrotropin is present in the circulation as a result of loss or decrease of the inhibiting circulating thyroid hormone.

Das Altersulkus an Magen und Zwolffingerdarm. By Konrad Spang. Pp. 103, with 36 illustrations. Georg Thieme, Karl Tauchnitzstr. 3, Leipzig C.1. (Russian Zone); Diemershaldenstrasse 47, Stuttgart-O (American Zone), 1948.

This thought-provoking monograph calls attention to the entity of ulceration of the stomach and duodenum in the older age groups. Observations on the clinical aspects and pathogenesis are presented, as derived from the study of 100 patients in the Ludolf Krehl Clinic in Heidelberg from 1944 to 1946.

The author sets forth his view of ulcer in the aged as a distinct clinical and pathogenic entity, differing from peptic ulcer. According to Spang, the former type occurs almost exclusively in those past 50 years of age, is usually a gastric ulcer and is almost always a large one (ulcers more than 5 cm. in diameter and 2 cm. in depth were encountered). The older the patient, the farther is the ulcer from the pylorus; the usual location is in the lesser curvature. The symptomatology is fairly definite: The symptoms are of short duration, the element of periodicity is lacking, there is little tendency to heal and the recovery period is long. Moreover, there is a tendency toward gastric hypoacidity. The most frequent and important complications are hemorrhage and perforation. Malignant transformation was observed in 1 patient of the 100 studied.

It is Spang's stated belief that these large gastric ulcers in older people are arteriosclerotic in origin, a hypothesis which is not new and which is compatible clinically with the low healing, as he remarks. A few photomicrographs are presented to show advanced sclerosis in the gastric arteries. The possibility that the surrounding vascular changes are secondary to the ulcer has not been excluded, however.

It is curious that the author's experience cannot be substantiated by those physicians in this country who have had wide experience with patients in all age groups and all walks of life with digestive complaints. This lack of confirmation calls to mind the geographic distribution of gastric ulcer, which seems to be commoner in Europe than in America.

The subject has been carefully and thoroughly studied and is presented with unusual clarity. This report will be of special interest both to gastroenterologists and to geriatricians.

Human Pathology. By Howard T. Karsner. Seventh edition. Price, $12. Pp. 927, with 584 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1949.

The first edition of "Human Pathology" by Howard T. Karsner was published in 1926. Twenty-three years later the seventh edition has come to hand. The first edition contained 980 single column pages and 463 illustrations, of which 20 were in color; the seventh edition contains 927 double column pages with 584 illustrations, including 22 in color. Over the years this book has assumed a more and more important place among textbooks of pathology, until gradually it has achieved preeminence. Students, professional pathologists, practicing physicians and surgeons have gone to it for accurate information about the known facts of the broad field of pathology and have found the information they wanted or a reference which filled their need. Dr. Karsner has always put into his book the best of the old and

the most promising of the new. His most recent additions include two excellent new chapters, which contribute greatly to the usefulness of the book. One is on diseases of the eye, written by J. Lowell Orbison and John E. L. Keyes, and the other, on diseases of the skin, by Herbert Z. Lund. The chapters on infectious diseases and on the liver have been largely rewritten; indeed, there are signs that most of the chapters have been revised. The index, which was poorly done in the sixth edition, is once more excellent, and the references are thoroughly up to date. A noteworthy feature is the excellence of the photographs of patients, organs and microscopic sections which illustrate the book. These are beautifully reproduced, which reflects much credit on the publisher. The book is published in a most satisfactory manner with the exception of its size and weight. But have there ever been medical textbooks which fit easily to hand?

The seventh edition of "Human Pathology" has appeared in the year that Dr. Karsner retired as Professor of Pathology and Director of the Institute of Pathology at Western Reserve University. It is indeed a fitting memorial to his years of teaching, investigation and writing in the Institute which he founded and raised to maturity. All his many students will be more than ever proud of "the Chief." In the opinion—be it prejudiced or not—of this particular former student, "Human Pathology" is more than ever the best book of its kind in our language.

The Eye and Its Diseases. Edited by C. Berens. Price, $16. Pp. 1,092, with 436 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1949.

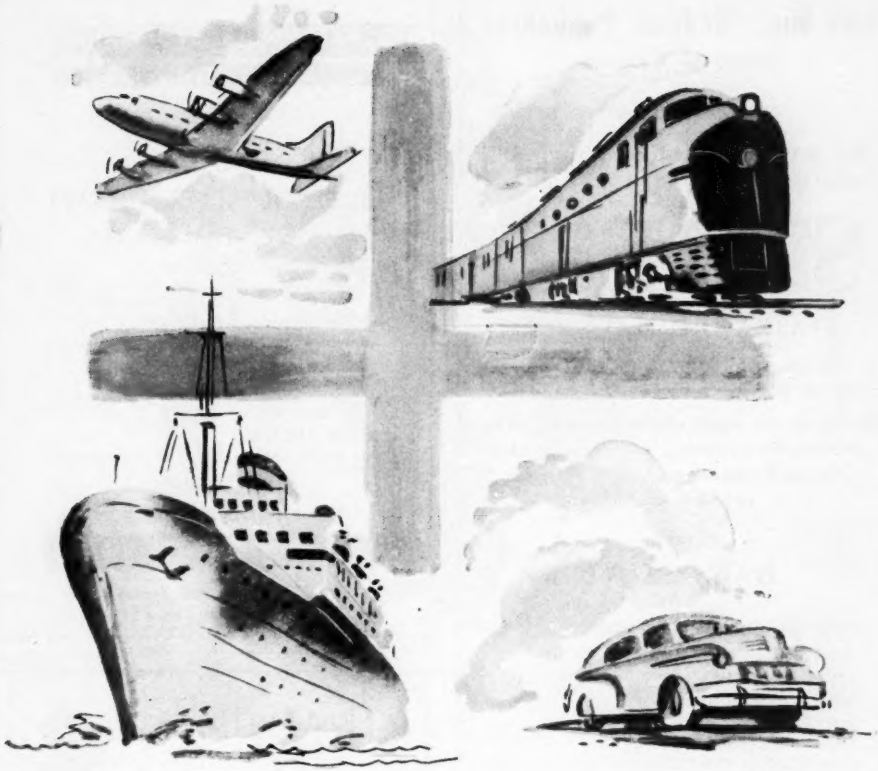
This widely used textbook, edited by one of today's leading ophthalmologists and written by 93 international authorities, has been revised and is now published in a second edition, dated 1949, the first having appeared in 1936. New chapters include those on illumination, physiologic chemistry and gonioscopy. Accepted advances in therapeutics, especially concerning the antibiotics, have been carefully evaluated. Bibliographies appearing at the ends of most of the chapters include the more recent references.

The internist will find several chapters of value to himself, in spite of the fact that the book was designed for students and teachers of ophthalmology. The account of the history of the ophthalmoscope, by Hardy, is fascinating reading, and his explanation of the technic of ophthalmoscopy is detailed and clear. The chapter on medical ophthalmology, written by Foster Moore, is worth serious study, but the reviewer wishes that in its revision some of the more recent concepts of hypertensive disease had been introduced. This want is satisfied, however, by Neames in his admirable review of diseases of the retina. The neurologist will read with profit the chapter by Casten on neuro-ophthalmology, in which disturbances in pupillary reactions and ocular rotations are explained in a thoroughly satisfying manner.

The numerous excellent chapters which deal with the various aspects of treatment will appeal to the ophthalmologist and will tempt him to add this textbook to his library.

NOTICE

The index for Volume 85 will be mailed with the July 1950 number.



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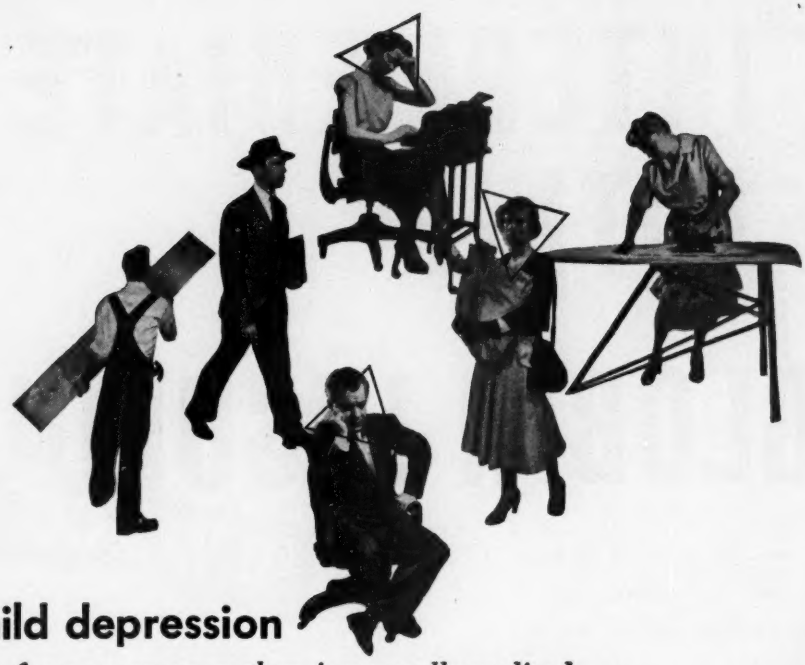

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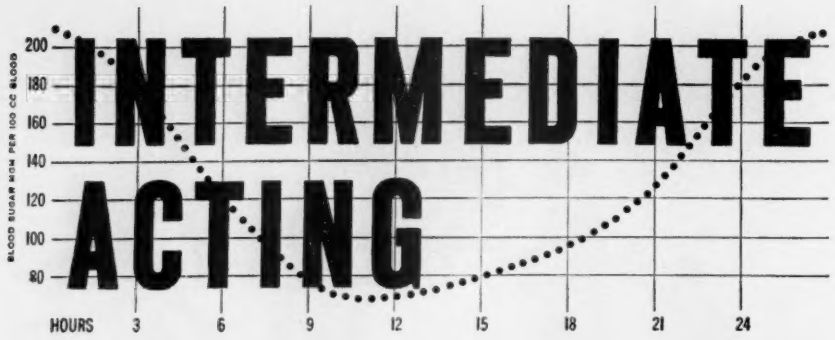

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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